Appeal No. 15-1871

United States Court of Appeals

for the

Federal Circuit

APOTEX INC.,

Appellant,

– v. –

WYETH LLC,

Appellee.

APPEAL FROM THE UNITED STATES PATENT AND TRADEMARK OFFICE, PATENT TRIAL AND APPEAL BOARD NO. IPR2014-00115

CORRECTED OPENING BRIEF FOR APPELLANT

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October 29, 2015

CERTIFICATE OF INTEREST FOR APOTEX INC.

Pursuant to Federal Circuit Rules 27(a)(7) and 47.4, counsel for Appellant Apotex Inc. certifies the following:

1. The full name of every party represented by me is: Apotex Inc.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is: The real parties-in-interest for this appeal are Apotex Inc., Apotex Corp., and Apotex Holdings, Inc.

3. All parent corporations and any publicly held companies that own 10% or more of the stock of any party represented by me are: Apotex Inc. is owned by Apotex Pharmaceuticals Holdings Inc., which is owned by Apotex Holdings Inc. Sherman Holdings Inc. and The Bernard Sherman 2000 Trust are parent corporations of Shermco Inc., which is parent of Sherfam, Inc., which is parent of Apotex Holdings Inc. None of the foregoing is a publicly traded company. No publicly held company owns 10 percent or more of the stock of Apotex Inc.

4. The names of all law firms and the partners or associates that have appeared for the parties now represented by us in the trial court or are expected to appear in this Court are: John Josef Molenda, Robert Greenfeld, and Katherine H. Johnson, all of Steptoe & Johnson LLP; Kenneth Burchfiel, Travis Ribar, Grant Shackelford, and Raja Saliba, all of Sughrue Mion, PLLC.

Dated: October 29, 2015

/s/ John Josef Molenda

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Patent Trial and Appeal Board	PTAB or Board
Apotex Inc.	Apotex
Wyeth LLC	Wyeth
U.S. Patent No. 7,879,828, A28-38	’828 patent
Chinese Patent Publication No. 1390550A, published January 15, 2003, A203-207 & A1393-1397 (English translation)	CN ’550
E. Pawelczyk et al., *Kinetics of Drug Decomposition. Part 74. Kinetics of Degradation of Minocycline in Aqueous Solution*, POL. J. PHARMACOL. PHARM. 34:409-421 (1982), A216-223	Pawelczyk
V. Naggar et al., *Effect of Solubilizers on the Stability of Tetracycline*, PHARMAZIE 29(2) 126-129 (1974), A224-225	Naggar
Petition for Inter Partes Review of U.S. Patent No. 7,879,828, Paper 1, A39-106	Petition
Decision on Institution, Paper 10, A1011-1021	Institution Dec.
Patent Owner Response, Paper 36, A1549-1614	Patent Owner Resp.
Petitioner’s Reply, Paper 60, A7090-7108 (public version)	Reply Br.
Record of Oral Hearing, Paper 89, A10219-10291	Hearing Tr.
Final Written Decision, Paper 94, A1-27	Final Written Dec.
Person of ordinary skill in the art	POSITA
Declaration of Mark L. Nelson, Ph.D., A107-202	Nelson Decl.
Nelson, Mark, *The chemistry and cellular biology of the Tetracyclines*, A321-385	Nelson Chapter
Verified Deposition Transcript of Mark L. Nelson, Ph.D., A1430-1548	Nelson Tr.
Expert Declaration of Lester A. Mitscher, Ph.D., A1624-1773	Mitscher Decl.
Videotaped Deposition of Lester Mitscher, Ph.D., A8390-8708 (public version)	Mitscher Tr.

SUMMARY OF RELATED CASES

No appeal in or from the same proceedings in the Patent Trial and Appeal Board ("PTAB" or "Board") was previously before this or any other appellate court. The '828 patent has been asserted in the following pending litigations: *Pfizer Inc. v. Fresenius Kabi USA, LLC*, No. 1:13-cv-01893-SLR (D. Del.); *Pfizer Inc. v. CFT Pharmaceuticals, LLC*, No. 1:14-cv-00781-SLR (D. Del.); *Pfizer Inc. v. Aurobindo Pharma Ltd.*, No. 1:14-cv-00872-SLR (D. Del.); *Pfizer Inc. v. Mylan Inc.*, No. 15-cv-00026-SLR (D. Del.); and *Pfizer Inc. v. Mylan Inc.*, No. 1:15-cv-00001-IMK (N.D. W. Va.).

JURISDICTIONAL STATEMENT

This appeal is from the Final Written Decision of the Patent Trial and Appeal Board dated April 20, 2015. Apotex timely filed a Notice of Appeal on June 18, 2015. This Court has jurisdiction under 35 U.S.C. § 141 and 28 U.S.C. § 1295(a)(4).

STATEMENT OF THE ISSUES

Whether the Board erred in holding that Claims 1-23 of U.S. Patent No. 7,879,828 (the "'828 patent") are not rendered obvious by CN '550,[1] Pawelczyk,[2] and Naggar.[3]

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[1] Chinese Patent Publication No. 1390550A, published January 15, 2003. A203-207 & A1393-1397 (English translation).

PRELIMINARY STATEMENT

The antibiotic composition at issue in this appeal is the paradigm of obviousness under *KSR*: an improvement-type composition containing a well-known tetracycline (tigecycline) to address two well-known stability problems [1] Chinese Patent Publication No. 1390550A, published January 15, 2003. A203-207 & A1393-1397 (English translation). (oxidation and epimerization). Specifically, the '828 patent is directed to a simple, three-part composition comprised of well-known components: (1) tigecycline antibiotic, which was developed in the 1990s, (2) lactose, and (3) hydrochloric or gentisic acid. Minocycline (a close chemical analog of tigecycline), lactose, and hydrochloric acid are all disclosed in the CN '550 reference, and various pH-related limitations are disclosed in Pawelczyk and Naggar. Not surprisingly, this Court recently affirmed the invalidation of a remarkably similar improvement-type, follow-on antibiotic composition in *Senju Pharmaceuticals Co. v. Lupin Ltd.*, 780 F.3d 1337 (Fed. Cir. 2015). Unfortunately, the Board in this case never got further than analyzing the issue of motivation, and even as part of that analysis, committed two crucial legal errors.

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[2] E. Pawelczyk et al., *Kinetics of Drug Decomposition. Part 74. Kinetics of Degradation of Minocycline in Aqueous Solution*, POL. J. PHARMACOL. PHARMA. 34:409-421 (1982) ("Pawelczyk"). A216-223.

[3] V. Naggar et al., *Effect of Solubilizers on the Stability of Tetracycline*, PHARMAZIE 29(2) 126-129 (1974) ("Naggar"). A224-225.

First, in violation of *Senju*, the Board erroneously imported an "epimeric stability" limitation into the claims, causing it to disregard CN '550, Apotex's primary reference, and Pawelczyk, one of Apotex's secondary references. Together with Naggar, these references render Claims 1-23 of the patent obvious.

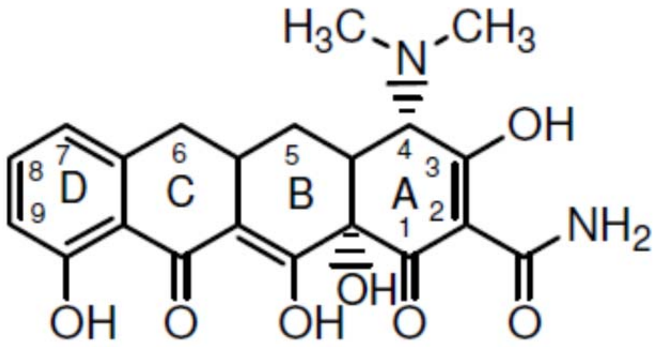
Second, in violation of *KSR* and its progeny, the Board limited its motivation analysis to only the problem the patentee was trying to solve rather than "any need or problem" in the field at the time of the invention. As such, the Board never addressed at least three of Apotex's motivation-related arguments, each of which provides a basis for a conclusion of obviousness.

For these reasons, this Court should reverse and/or vacate the Board's judgment of non-obviousness and remand for further proceedings.

I. STATEMENT OF THE FACTS

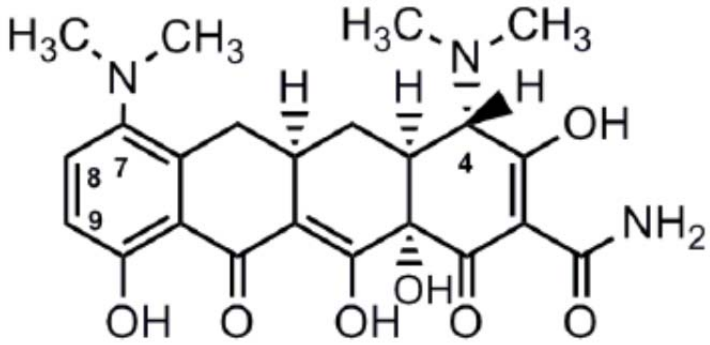
A. Overview of the Tetracycline Family of Antibiotics

In the mid-1940s, the tetracycline family of antibiotics was discovered to be an effective treatment against various types of bacterial infections. A1645-46 (Mitscher Decl. ¶ 50); A119-20 (Nelson Decl. ¶ 13); A329-330 (Nelson Chapter). Tetracycline antibiotics derive their name from the fact that they share the same core, four-ring chemical structure (denominated from A to D):



A121 (Nelson Decl. ¶ 15).

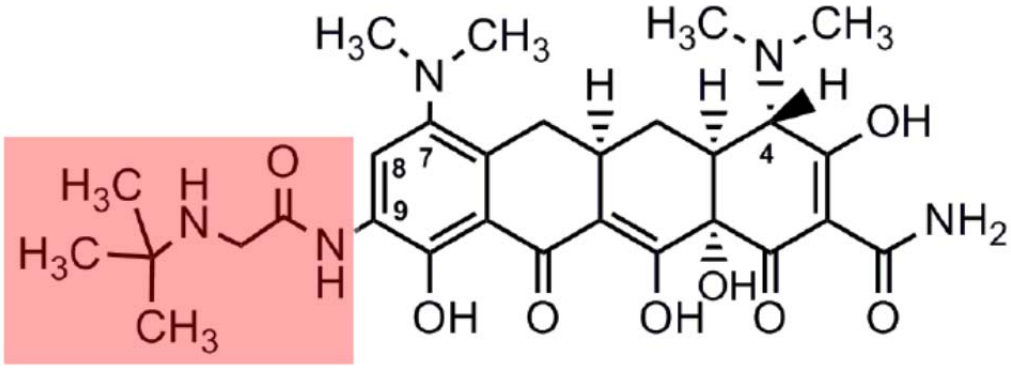
Due to bacterial resistance against the first generation of tetracyclines, in the 1960 scientists synthesized a second generation of tetracyclines, one of which was minocycline. A1645-46 (Mitscher Decl. ¶ 50). The chemical structure of minocycline is depicted below:



A123-24 (Nelson Decl. ¶ 19).

Due to continued problems with bacterial resistance, in the late 1990s a third-generation tetracycline known as tigecycline was synthesized through chemical modification of minocycline. A31 (’828 patent, col. 1, ll. 22-44); A120-21 (Nelson Decl. ¶ 14); A1646-47 (Mitscher Decl. ¶ 52). Tigecycline differs from

minocycline ***only*** with respect to a single substituent group at the C9 position on the D ring, which is depicted in pink in the figure below. A1646-47 (Mitscher Decl. ¶ 52); A123-24 (Nelson Decl. ¶ 19) (shading added); *see also* A31 (col. 2, ll. 57-67).



Not surprisingly, the ’828 patent refers to tigecycline and minocycline as “chemical analogs” of each other due to their high degree of structural similarity. A31 (col. 1, ll. 22-23). Tigecycline compositions with improved stability-related properties are the focus of the ’828 patent.

B. U.S. Patent No. 7,879,828

1. The Specification

The ’828 patent is directed to “improved tigecycline compositions and methods for making such compositions.” A31 (col. 1, ll. 7-8). As described in the specification, the alleged invention, which purports to possess enhanced stability in both the solid and solution states, is a simple composition comprised of three well-

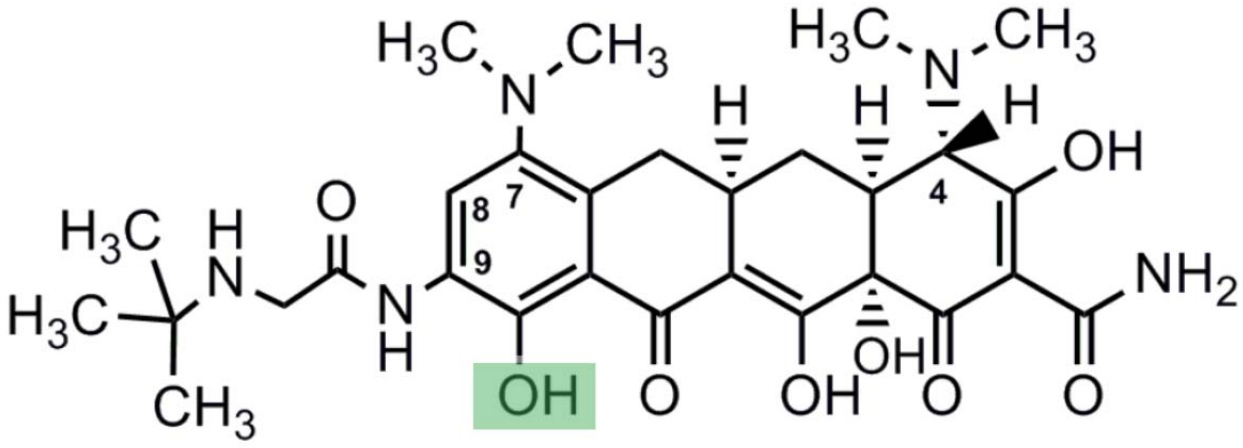
known components: (1) tigecycline antibiotic, (2) a "suitable carbohydrate," and (3) an acid or buffer. *Id.* (col. 1, ll. 8-11). Each of these components is discussed in detail below.

a. Tigecycline and Its Stability Problems

As acknowledged in the '828 patent and discussed above, tigecycline is "a ***known*** antibiotic in the tetracycline family and a chemical analog of minocycline." A31 (col. 1, ll. 21-22) (emphasis added). The specification teaches that, like minocycline and other tetracyclines, tigecycline suffered from two well-known types of degradation: oxidation and epimerization. *Id.* (col. 1, ll. 15-18; col. 2, ll. 23-50); A1651 (Mitscher Decl. ¶ 59); A8448 (Mitscher Tr. 59:2-13) ("Q: So the problems of oxidation and epimerization were well known and would have been expected for tigecycline as well as the other tetracyclines? A: Yes."); A8456 (Mitscher Tr. 67:5-16).

As for oxidation, the specification discloses that this process can occur in several of the key steps in the making and using of tigecycline, including manufacturing, storage, and administration of the drug. A31 (col. 1, l. 46 to col. 2, l. 25); *see also id.* (col. 2, ll. 25-27) ("Under current manufacturing, storage, and administration conditions, the most prevalent form of degradation is via oxidation."). The specification teaches that tigecycline is particularly vulnerable to degradation via oxidation because "[i]t possesses a phenol moiety, and it is ***well***

known in the art of organic chemistry that phenols are particularly prone to oxidation." *Id.* (col. 2, ll. 27-32) (emphasis added). The phenol moiety is shaded in green below:

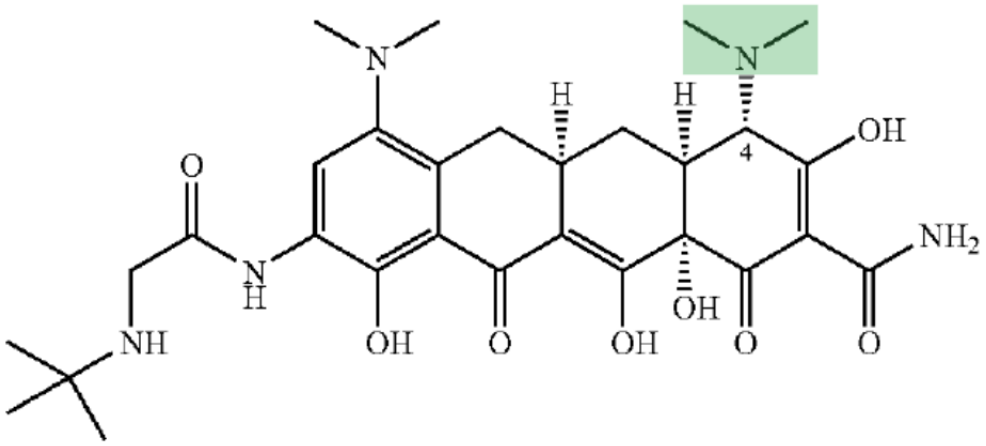


A124 (Nelson Decl. ¶ 19) (shading added).

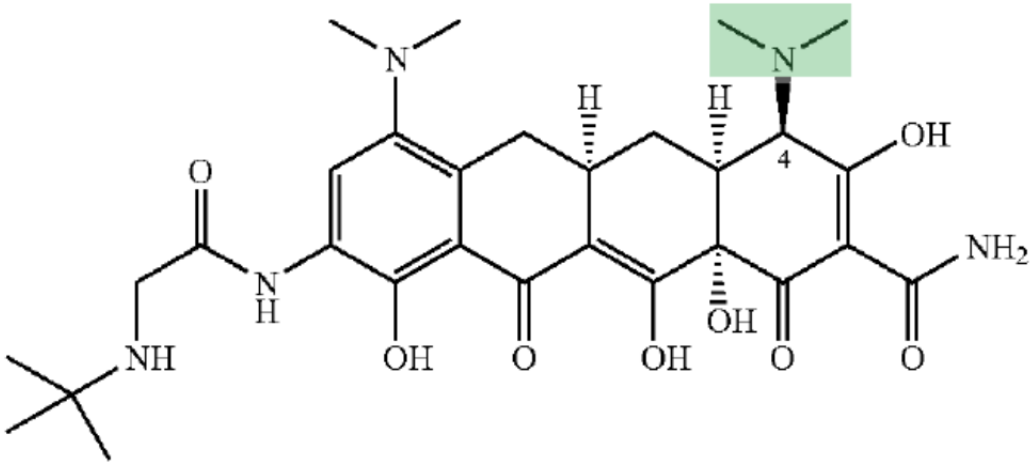
While oxidative degradation can be reduced if the pH of the tigecycline solution is sufficiently lowered, A31 (col. 2, ll. 43-47), at lower pHs, the well-known epimerization process occurs, *id.* (col. 2, ll. 47-50); *see also id.* (col. 3, ll. 31-33) ("Epimerization is a known degradation pathway in tetracyclines generally, although the rate of degradation may vary depending upon the tetracycline."). Epimerization occurs when the spatial arrangement of atoms around a carbon atom changes. *See* A148-49 (Nelson Decl. ¶ 66, bullet 5). In this case, the dimethylamino group of tigecycline, shaded in green below, can change its relative orientation in space, changing from its "cis" form (Formula I), in which the dimethylamino group points downward (into the paper, shown by the ⩇ symbol) to

its "trans" form (Formula II), in which the dimethylamino group points upward (out from the paper, shown by the ▼ symbol). *Id.*

FORMULA I



FORMULA II



A31-32 (col. 2, l. 51 to col. 3, l. 18); A1668-69 (Mitscher Decl. ¶ 93); A121-22 (Nelson Decl. ¶¶ 15-16). Because the "trans" form lacks the efficacy of its "cis" counterpart, it is viewed as an unwanted degradation product. A32 (col. 3, ll. 19-22).

b. Carbohydrate

The specification teaches that a wide range of carbohydrates may be used as part of the claimed composition. "Any carbohydrate capable of reducing epimer formation in the invention is a suitable carbohydrate and this invention is not limited to compositions employing those carbohydrates specifically identified." A33 (col. 5, ll. 48-51). The specification discloses a laundry list of well-known carbohydrates, including lactose, mannose, sucrose, and glucose, along with monosaccharides, disaccharides, polysaccharides, and various sugar derivatives. *Id.* (col. 5, ll. 14-26, 52-64). Of all of these carbohydrates, lactose is most preferred, *id.* (col. 5, l. 20), and all 23 of the claims at issue are limited to lactose.

c. Acids

The specification likewise teaches that several well-known, pharmaceutically acceptable acids may be used as part of the claimed composition to minimize oxidation. Such acids include hydrochloric acid, gentisic acid, lactic acid, acetic acid, and phosphoric acid. A33 (col. 6, ll. 2-5); A3175-76 (9/21/09 Office Action) (Examiner noting that hydrochloric acid is a well-known acid). These acids need only be capable of adjusting the pH of a tigecycline/suitable carbohydrate solution "to between about 3.0 to about 7.0, about 4.0 to about 5.0, or about 4.2 to about 4.8." A33 (col. 5, l. 65 to col. 6, l. 2). Independent Claim 1 is

limited to hydrochloric acid or gentisic acid; independent Claim 12 is limited to hydrochloric acid.

2. The Claims

The ’828 patent contains 23 composition claims, all of which are at issue in this appeal. Independent Claim 1 is representative:

> 1. A composition comprising [1] tigecycline, [2] lactose, and [3] an acid selected from hydrochloric acid and gentisic acid,
>
> wherein [4] the molar ratio of tigecycline to lactose is between about 1:0.2 and about 1:5 and [5] the pH of the composition in a solution is between about 3.0 to about 7.0.

Claim 1 recites a three-part composition comprising tigecycline, lactose, and either hydrochloric acid or gentisic acid, with the molar ratio of tigecycline to lactose being between about 1:0.2 and about 1:5 and the pH of the composition being between about 3.0 to about 7.0. The other independent claim of the ’828 patent, Claim 12, is identical to Claim 1 but is limited to hydrochloric acid.

The dependent claims recite additional limitations including a lyophilized composition (Claim 2), a solid form composition (Claims 3, 18, 19, 20, 21, 22, and 23), narrower pH ranges (Claims 4, 5, 10, 11, 14, 15, 16, and 17), or narrower molar ratios of tigecycline to lactose (Claims 9 and 13). Claims 6, 7, and 8 further limit the acid recited in Claim 1 to only hydrochloric acid.

Examination of these claims reveals an important point that is key to resolution of this appeal: while the specification describes solving the problems of

oxidative degradation and epimerization in tigecycline compositions, A32 (col. 4, ll. 49-59), notably absent are ***any*** claim limitations directed to either oxidation or epimerization.

C. The Prior Art

1. Tigecycline

First, as explained above, tigecycline was known, as was its structural similarity to minocycline. A31 (col. 1, ll. 22-23) ("Tigecycline is a known antibiotic in the tetracycline family and a chemical analog of minocycline."). Second, tigecycline was known as an improved antibiotic, showing success against bacteria such as against *Staphylococcus aureus* that had developed resistance to earlier-generation antibiotics. *Id.* (col. 1, ll. 23-27).

2. Chinese Patent Publication No. 1390550A[4]

CN '550 is a Chinese patent application directed to "a lyophilized minocycline hydrochloride powder injection and its method of preparation." A1393 (CN '550 Title, Summary). CN '550 was published on January 15, 2003,

[4] References to CN '550 herein are to the corrected translation. A1393-97. The original translation submitted with the Petition included errors related to (1) the mis-translation of "lyophilized powder supporting agent" as "excipient" and (2) an additional recitation of lactose in the specification. Since lactose is disclosed in Claim 5 of CN '550 in both translations, none of these errors is pertinent to this appeal.

more than one year before the earliest claimed benefit date of the ’828 patent, and is prior art under 35 U.S.C. § 102(b).

The three-part antibiotic composition disclosed in CN ’550, which is stable to light, heat, oxygen, and water, A1393, 1395, bears remarkable similarity to the stable, three-part antibiotic composition claimed in the ’828 patent. First, both compositions are comprised of a tetracycline family member – tigecycline in the case of the ’828 patent and its “chemical analog” minocycline in the case of CN ’550. A1393-97. Second, the ’828 composition is comprised of the carbohydrate lactose, while CN ’550 is comprised of a lyophilized powder supporting agent, which can likewise include various carbohydrates such as lactose. A1394. Third, the ’828 composition is comprised of an acid such as hydrochloric acid, while the CN ’550 composition is similarly comprised of a pH adjusting agent such as hydrochloric acid. A1394-96.

The claims of CN ’550 disclose various combinations of the three main ingredients. Of particular significance is Claim 5, which specifically discloses a stable minocycline composition containing lactose:

> 5. A lyophilized ***minocycline hydrochloride*** powder injection and its method of preparation according to claim 1 or claim 3, characterized in that: The lyophilized powder supporting agent is a soluble support,

> selected from mannitol, glucose, NaCl, dextran, ***lactose***, and hydrolyzed gelatin.[5]

A1394 (emphasis added); A1572 (Patent Owner Resp.). Claim 6, which depends from Claim 1, recites that the pH adjusting agent is "an inorganic acid such as ***hydrochloric acid*** . . . ."; Claim 4, which depends from Claims 1 or 3, states that the pH may be between 0.1 and 7.5; and Claim 7, which depends from Claim 4, states that the "most appropriate" pH is from 2.0 to 3.5. A1394 (emphasis added).

CN '550 further discloses three embodiments with differing lyophilized powder supporting agents and differing pH adjusting agents; in all three of the preparations, the mass ratio of minocycline hydrochloride to lyophilized powder supporting agent is 108 to 210 grams. A1396-97. When the mass ratios are converted to molar ratios using corresponding molecular weights, the ratio is about 1:5 for the mannitol composition and about 1:0.02 for the dextran composition. A166-67 (Nelson Decl. ¶ 102); A1737 (Mitscher Decl. ¶ 197); A1468 (Nelson Tr. 148:15-17) (hydrolyzed gelatin does not have a distinct molecular weight).

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[5] Claim 1 of CN '550, A1394, provides:

> 1. A lyophilized minocycline hydrochloride powder injection, characterized in that: This lyophilized powder for injection is made of minocycline hydrochloride, a lyophilized powder supporting agent, and a pH adjusting agent, and their parts by weight are: 0.05-10 parts minocycline hydrochloride, 0-100 parts lyophilized powder supporting agent, and a suitable amount of pH adjusting agent.

Taken together, CN ’550 itself renders obvious all or at least a substantial majority of the ’828 patent claims: independent Claims 1 and 12, dependent claims directed to lyophilization (Claim 2), a solid form composition (Claims 3, 18, 19, 20, 21, 22, and 23), only hydrochloric acid (Claims 6, 7, and 8), and molar ratios of tigecycline to lactose between 1:1.6 and 1:3.3 (Claims 9 and 13). To the extent that CN ’550’s disclosure of pH ranges from 0 to 7.5 and 2.0 to 3.5 do not render obvious the claims reciting pH ranges from 4.0 to 6.0 (Claims 4, 5, 10, 11, 14, 15, 16, and 17), Pawelczyk and Naggar fill in that small gap.[6]

3. Pawelczyk et al., *Kinetics of Drug Decomposition*

Pawelczyk is a scholarly article describing the kinetics of oxidative stability of minocycline at acidic pH. A216 (Abstract). Pawelczyk was published in 1982, long before the earliest claimed benefit date for the ’828 patent. *Id.* Like CN ’550, it is prior art under 35 U.S.C. § 102(b).

Pawelczyk discloses that minocycline can be degraded by both epimerization and oxidation. *Id.* (p. 409). Pawelczyk recognized that if the pH of

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[6] The ’828 patent addresses CN ’550 (“Chinese Patent Application CN 1390550A”), admitting that it discloses (1) minocycline, (2) a “caking agent” such as the carbohydrate mannitol, and (3) an acid to minimize oxidative degradation. A32 (col. 4, ll. 22-25). Nonetheless, the ’828 patent dismisses the reference because (1) it does not contain tigecycline, (2) it does not teach that a carbohydrate could be used to reduce oxidation or epimerization of minocycline at low pH, and (3) minocycline and tigecycline epimerize differently. *Id.* (col. 4, ll. 25-33). Significantly, distinctions (2) and (3) have nothing to do with any limitation recited in the ’828 patent claims.

a minocycline solution is lowered below about 5, oxidative stability increases. A220 (p. 417) ("Oxidation is a predominant process of [minocycline] degradation above pH 5."); A128 (Nelson Decl. ¶ 27). Pawelczyk discloses using various acids, including hydrochloric acid, to adjust the pH downward to reduce oxidation, A218, 220 (pp. 413, 416-17), including a variety of aqueous solutions below pH 5.5. A216, 218 (pp. 409, 413); A170-71 (Nelson Decl. ¶ 111).

Combined with CN '550's broader range of 0 to 7.5, Pawelczyk teaches to narrow the high end of that range to less than 5 to minimize oxidation for more optimal performance.

4. Naggar et al., *Effect of Solubilizers on the Stability of Tetracycline*

Like Pawelczyk, Naggar is another scholarly article that describes stability of tetracyclines at acidic pH, but differs from Pawelczyk in that it focuses on epimeric stability. A224 (Naggar, Abstract). Naggar was published in 1974, long before the earliest claimed benefit date for the '828 patent. *Id.* It is also prior art under 35 U.S.C. § 102(b).

Naggar discloses that tetracycline epimerization may occur within a pH range of from 2 to 6, with the most rapid epimerization between 3 and 4. A224 (p. 126); A129 (Nelson Decl. ¶ 31). Naggar also discloses the use of solubilizers to reduce epimerization in tetracyclines. A224 (p. 126). Combined with CN '550's

broader range of 0 to 7.5, Naggar teaches to narrow the low end of that range to greater than 4 to minimize epimerization for more optimal performance.

Taken together, Pawelczyk and Naggar teach how to stabilize tetracyclines vis-à-vis both oxidation and epimerization. Pawelczyk teaches lowering tetracycline pH below 5 for oxidative stability, Naggar teaches not to lower tetracycline pH below 4 to avoid rapid epimerization. Thus, the combined disclosures of Pawelczyk and Naggar indicate that tetracyclines are most stable to both of the major degradation pathways – oxidation and epimerization – at a pH of between 4 and 5. A171-72 (Nelson Decl. ¶ 113).

D. Procedural History at the Board

1. Institution Decision

On November 1, 2013, Apotex filed an IPR petition seeking review of Claims 1-23 of the ’828 patent. A38.2. Apotex raised seven grounds of unpatentability, each asserting that Claims 1-23 were unpatentable as obvious. A1014-15 (Institution Dec.). On April 21, 2014, the Board issued an order instituting review of those claims based upon Ground 2: CN ’550 in view of Pawelczyk and Naggar. A1018. The Board declined to institute review based on the other grounds. A1019.

In its Institution Decision, the Board was persuaded by Apotex’s argument that the structural similarity of minocycline and tigecycline, coupled with the fact

that both molecules undergo epimerization at the C4 dimethylamino group by the same reaction, provide a reason to substitute tigecycline for minocycline in the formulation of CN '550. A1017-18. The Board was similarly persuaded by Apotex's arguments that, *inter alia*, a person of ordinary skill in the art would have been motivated to reduce solution pH to below about 5 to avoid oxidative degradation as taught by Pawelczyk and would have selected a pH of 4-5 to limit epimeric degradation as taught by Naggar. *Id.* Finally, the Board was persuaded by Apotex's obviousness arguments concerning the various molar ratios of tigecycline and lactose recited in the claims. A1018.

2. Final Written Decision

Following an oral hearing on January 23, 2015, the Board issued its Final Written Decision on April 20, 2015. The Board held that Apotex did not show by a preponderance of the evidence that Claims 1-23 of the '828 patent were unpatentable as obvious. A3. The Board determined that (1) a person of ordinary skill in the art ("POSITA") would not have been motivated to substitute tigecycline for minocycline in the formulation disclosed in CN '550, A11-14, and (2) a POSITA would not have been motivated to combine CN '550 with Pawelczyk and Naggar to address tigecycline's instability problems by using lactose, A15-22.

With respect to the substitution issue, the Board found that Apotex had not "adequately" established that a POSITA "would have had reason to believe that

tigecycline, rather than minocycline, would have been similarly stable in the formulation disclosed in CN '550." A14; *see also* A12-14. The Board stated, "Petitioner's contentions in this regard are insufficient because they presume that a person of ordinary skill in the art would have recognized that the compositions disclosed in CN '550 were stable against epimerization." *Id.* The Board made this determination despite acknowledging that "Petitioner is correct that the claims do not recite epimeric stability and therefore obviousness of the claims can be demonstrated without a showing of epimeric stability in the prior art." A14; *see also* A13-14 (summarizing Apotex's arguments that whether a POSITA would have recognized that CN '550's compositions were epimerically stable is legally irrelevant, that the claims at issue are directed to compositions ***not*** methods of stabilizing, and that the reason for the substitution could be ***any*** reason, not just reduction in epimerization). In essence, the Board tied the issue of motivation to substitute to epimerization and disregarded Apotex's motivation arguments based upon structural similarity.

With respect to using lactose to stabilize a tigecycline composition, the Board found that there would be no motivation to combine CN '550 with Pawelczyk and Naggar, again focusing heavily on the issue of epimerization. As pertinent here, the Board found that while CN '550 discloses stability against light, heat, oxygen, and water, it does not disclose epimeric stability, and Pawelczyk

does not mention epimerization. A15-16. The Board also found no support for Dr. Nelson's opinion that a POSITA would have appreciated that CN '550's disclosure of a lyophilized powder that is stable under acidic conditions by various saccharides would have included stability against C4 epimerization, particularly given that the reference does not explicitly mention epimerization. A16-17. The Board additionally found that CN '550's disclosure of compositions that are therapeutically effective does not necessarily suggest that those compositions are stable against epimerization. A18-20.

Having determined that there was no motivation to substitute tigecycline for minocycline in CN '550, and no motivation to combine CN '550 with Pawelczyk and Naggar, the Board concluded that Claims 1-23 were not obvious. *See* A22.

II. SUMMARY OF THE ARGUMENT

The Board made two fundamental errors in holding that Claims 1-23 were not obvious.

First, the Board erred by importing an epimeric stability limitation into these composition claims, contrary to longstanding Federal Circuit law recently reiterated in *Senju*. This reversible error caused the Board to discredit CN '550 and Pawelczyk for purportedly failing to teach epimeric stability. Together with Naggar, CN '550 and Pawelczyk render Claims 1-23 of the patent obvious.

Second, the Board erred by failing to consider motivations beyond the problem the patentee was trying to solve (minimizing epimerization), contrary to *KSR* and well-established Federal Circuit precedent. *See, e.g.*, *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1368 (Fed. Cir. 2012) (stating that "[w]e have repeatedly held that the motivation to modify a prior art reference to arrive at the claimed invention need not be the same motivation that the patentee had"). As a result, the Board did not address at least three of Apotex's motivation-related arguments. First, the structural similarity of tigecycline and minocycline, including the identity of their A and B rings and the fact that they undergo epimerization at the same C4 dimethylamino group by the same reaction, would have led a POSITA to substitute minocycline in CN '550 with tigecycline. Second, a POSITA would have been motivated to combine the references to optimize the CN '550 pH ranges of 0-7.5 and 2.0-3.5 and thereby achieve the specific pH ranges recited in the dependent claims, because it was well known in the prior art that oxidation and epimerization plagued tetracyclines at differing pH levels. Third, a POSITA would have been motivated to modify the pH ranges in CN '550 to arrive at the pH ranges recited in the dependent claims, because those pH ranges were commonly employed in conventional injection solutions. Each of these arguments provides a basis to render the claims obvious.

III. ARGUMENT

A. Standard of Review

Obviousness is a question of law, based on factual determinations. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). This Court reviews the Board's ultimate determination of obviousness *de novo*, and the factual findings underlying that determination are reviewed for substantial evidence. *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1280 (Fed. Cir. 2015). Substantial evidence is "less than the weight of the evidence but more than a mere scintilla of evidence." *In re Morsa*, 713 F.3d 104, 109 (Fed. Cir. 2013), *cert. denied*, 134 S. Ct. 1317 (2014). An unexpired patent that is the subject of an IPR is not presumed valid, *Cuozzo*, 778 F.3d at 1276, and the petitioner must prove "unpatentability by a preponderance of the evidence," 35 U.S.C. § 316(e).

B. The Board Erred by Importing an "Epimeric Stability" Limitation Into the Claims

As an initial matter, the Board made a key legal error by importing an epimeric stability limitation into the 23 composition claims, thereby improperly adding an extra limitation for Apotex to meet with its prior art references. This error caused the Board to discredit Apotex's primary obviousness reference, CN '550, as well as one of Apotex's secondary references, Pawelczyk, and ultimately resulted in the Board's erroneous conclusion of non-obviousness.

1. Under *Senju*, It Is Reversible Error to Import Limitations Into the Claims as Part of an Obviousness Analysis

It is black letter law that limitations may not be imported from the specification into the claims, including as part of an obviousness analysis. *Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1346 (Fed. Cir. 2015) (declining to import into a composition claim a limitation denoting the function of the composition); *see also, e.g., EPOS Techs. Ltd. v. Pegasus Techs. Ltd.*, 766 F.3d 1338, 1341 (Fed. Cir. 2014) (recognizing the long-held rule that one should not read limitations from a preferred embodiment into the claims); *accord Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005) (en banc).

This Court recently applied this legal principle in *Senju*. In *Senju*, the Federal Circuit affirmed a district court's determination that certain composition claims directed to an eye drop mixture of gatifloxacin, a fluoroquinolone antibiotic, were invalid as obvious in view of prior art references disclosing quinolone antibacterial agents. 780 F.3d at 1343, 1346-47. Two sets of claims were at issue – a method claim (Claim 6) that included a corneal permeability limitation and composition claims (Claims 12-16) that did not. Regarding the composition claims, the district court declined to consider evidence regarding corneal permeability, because this quality was not recited in the composition claims. *Id.* at 1344. On appeal, the patent owner argued that corneal permeability was relevant to those claims, because they embodied the method of Claim 6, and corneal

permeability was the purpose of the claimed compositions. 780 F.3d at 1344-45. This Court affirmed, holding that evidence relating to corneal permeability was irrelevant to an obviousness analysis involving the composition claims that did not include a corneal permeability limitation:

> Many of appellants' arguments on the lack of reasons to combine the teachings of these three patents rely on the fact that they do not disclose anything about corneal permeability of gatifloxacin solutions. As discussed above, this is not a limitation of claims 12-16 and, therefore, is ***not relevant*** to the obviousness determination.

Id. at 1346-47 (emphasis added). Accordingly, this Court affirmed the district court's decision holding the composition claims invalid as obvious. *Id.*

The *Senju* case thus stands for the proposition that any purported failure of the prior art to disclose the particular purpose of claimed compositions is "not relevant" to, and does not avoid, a finding of obviousness as to such claims that do not recite that purpose. *Id*.

2. The Board Violated *Senju* By Importing an "Epimeric Stability" Limitation Into the Composition Claims, Causing It to Improperly Discredit CN '550 and Pawelczyk

The Board violated *Senju*, and the long line of precedent upon which it is based, by importing an epimeric stability limitation into the 23 composition claims at issue here. Independent Claims 1 and 12 are directed to compositions comprising tigecycline, lactose, and hydrochloric or gentisic acid, including particular molar ratios of tigecycline/lactose and pH ranges. The dependent claims

recite limitations directed to lyophilization, a solid form composition, narrower molar ratios, and narrower pH limitations. ***None*** of the claims recites any limitation directed to epimerization or epimeric stability, nor is there any recitation of any quality or objective relating to stability or degradation of any sort.

Despite the absence of any epimeric quality in the claims, and the Board's acknowledgement that "the claims do not recite epimeric stability," A14 (Final Written Dec.), the Board unduly focused on this concept; a review of the Board's Final Written Decision reveals that it is replete with references to epimerization and epimeric stability. This undue emphasis led the Board to improperly discredit both CN '550 (primary reference) and Pawelczyk (secondary reference), repeatedly criticizing both references for an alleged lack of teachings concerning epimerization or epimeric stability. *See, e.g.*, A13 (Final Written Dec.) ("As is discussed below, Petitioner has not established that a person of ordinary skill in the art would have known from the CN '550 disclosure that the described minocycline compositions were suitable against epimerization."); A15 ("[T]here are no statements from which a person skilled in the art would understand that the CN '550 formulations were epimerically stable."); A15-16 ("Indeed, neither CN '550 nor Pawelczyk mention epimerization at all."). The Board similarly discounted the epimerization arguments of Apotex's expert, Dr. Nelson, because it did not believe that CN '550 taught epimerically stable minocycline compounds. A13; *see also*

A16 (discounting Dr. Nelson's explanation why a POSITA would understand CN '550's compositions to be epimerically stable).[7]

Ultimately, the Board's belief that epimeric stability should be read into the claims, and that CN '550 and Pawelczyk must disclose that "limitation" in order to render Claims 1-23 obvious, led to its erroneous conclusion of non-obviousness in plain violation of *Senju*. *Senju*, 780 F.3d at 1346.

C. The Board Erred in Failing to Consider Motivations Beyond the Problem the Patentee Was Trying to Solve

In violation of both Supreme Court and Federal Circuit precedent, the Board made a second legal error in its obviousness analysis by failing to consider "any need or problem" in the field at the time of the invention. Rather, the Board focused narrowly on the epimerization problem the patentee was trying to solve. As explained below, this error led the Board to erroneously disregard several key motivation-related arguments raised by Apotex.

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[7] It should be noted that the Board essentially adopted Wyeth's improper argument that an epimerization limitation should be imported into the claims. Despite acknowledging that the claims do not mention epimerization or oxidation, A8425 (Mitscher Tr. 36:4-13); *see also* A8638 (Mitscher Tr. 249:5-17) (the claims "don't specifically say . . . epimerization"), Dr. Mitscher admitted that when he prepared his opinions in this case for Wyeth, he concluded that "the composition defined in Claim 1 was a composition that ***had to be*** stable against epimerization." A8427 (Mitscher Tr. 38:9-17) (objection omitted) (emphasis added). In other words, Dr. Mitscher conceded that his validity opinions were based upon the legally improper assumption that the Claim 1 composition included a ***requirement*** that it be stable against epimerization.

1. Under *KSR*, *Any* Need or Problem May Provide a Motivation to Combine

In *KSR*, the Supreme Court specifically addressed the issue of whether, in determining obviousness, courts and examiners should focus only on the problem the patentee was attempting to solve. 550 U.S. at 420. The Court explicitly held that such a narrow view was erroneous, because "neither the particular motivation nor the avowed purpose of the patentee controls." *Id.* at 419. Instead, a court may consider "inferences and creative steps" that a POSITA would employ, *id.* at 418, including the "simple substitution of one known element for another," *id.* at 417. In fact, "***any*** need or problem" in the field at the time of invention and addressed by the patent can provide a reason to combine prior art elements. *Id*. at 420 (emphasis added).

The Federal Circuit has consistently followed this approach since *KSR*. For example, in *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362 (Fed. Cir. 2012), the claims were directed to "a method for treating allergic eye disease in humans comprising stabilizing conjunctival mast cells by topically administering a [therapeutically effective amount of] an olopatadine composition." *Id.* at 1363. The prior art reference asserted by appellant had shown the use of olopatadine in guinea pigs' eyes as an antihistamine, but not as a mast cell stabilizer. *Id.* at 1365. The Federal Circuit reversed the district court's holding of non-obviousness, holding in pertinent part that stabilization of mast cells, the problem disclosed in

the patent, was not the only motivation that could be used, and the antihistaminic motivation in the prior art sufficed to find the patent obvious. The Court stated, "We have repeatedly held that the motivation to modify a prior art reference to arrive at the claimed invention need not be the same motivation that the patentee had." *Id.* at 1368-69 (citing *KSR*, 550 U.S. at 420; *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006); *In re Beattie*, 974 F.2d 1309, 1312 (Fed. Cir. 1992); *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006)).

2. The Board Violated *KSR* and Its Progeny By Disregarding Other Motivations Beyond the Epimerization Problem

In this case, the Board ignored Supreme Court and Federal Circuit precedent by failing to consider motivations beyond the epimerization problem the patentee was trying to solve. *See, e.g.*, A13 (Final Written Dec.) (declining to substitute tigecycline for minocycline because CN '550 does not explicitly disclose epimerization); A16-17 (declining to combine CN '550, Pawelczyk, and Naggar because CN '550 disclosed stability to light, heat, oxygen and water but not epimerization).[8]

[8] Wyeth contributed to this problem by counseling its experts to view obviousness through the narrow, pre-*KSR* framework of focusing only on the problem the inventors faced. *See KSR*, 550 U.S. at 407 (discussing narrow, pre-*KSR* inquiry). For example, one of its experts, Dr. Mitscher, was assigned the task of determining whether "a person of ordinary skill in the art ('POOS') trying to solve the known epimerization and oxidation problems would have found it obvious to make and use the particular claimed combination of tigecycline, lactose,

In fact, Apotex provided at least three motivations other than epimeric stability that were never addressed by the Board. First, Apotex argued that the structural similarity of tigecycline and minocycline, including the identity of their A and B rings and the fact that they undergo epimerization at the same C4 dimethylamino group by the same reaction, would have led a POSITA to substitute minocycline in CN '550 with tigecycline. A13; *see also* A85 (Petition) (arguing that using lactose to stabilize tigecycline against "degradation in acidic solutions involves no more than the simple substitution of tigecycline for its known analog minocycline in the prior art CN '550 composition," since tigecycline is an improved tetracycline); *see also Senju*, 780 F.3d at 1347 (finding motivation to combine because later generation drug, gatifloxacin, was recognized in the art as a mere improvement of an earlier-generation drug); *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) (noting that it is presumed that structurally similar molecules possess similar properties). While Apotex's argument was noted in the Final Decision, the merits of this argument were never addressed by the Board.

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and hydrochloric or gentisic acid at the pH ranges and molar ratios claimed in the '828 patent claims." A1636 (Mitscher Decl. ¶ 29). Wyeth then encouraged the Board to take this same position.

Second, the Board ignored Apotex's argument that a motivation to combine the references would have arisen to optimize the CN '550 pH ranges of 0-7.5 and 2.0-3.5 and thereby achieve the specific pH ranges recited in the dependent claims, because it was well known in the prior art that oxidation and epimerization plagued tetracyclines at differing pH levels. A7098 (Reply Br.); A10241-42 (Hearing Tr.). Pawelczyk teaches tetracycline solutions having pH below 5 to control oxidative degradation, and Naggar teaches tetracycline solutions having pH above 4 to control epimeric degradation. Apotex argued that these "two references converge on a range of about 4 to 5 as the most stable composition both from an oxidation and epimerization characteristics." A10242 (Hearing Tr.); *see also* A7099-7100 (Reply Br.).

Third, Apotex also argued that a POSITA would have been motivated to modify the pH ranges in CN '550 to arrive at the pH ranges recited in the dependent claims, because those pH ranges were commonly used in conventional injection solutions. A7100. Apotex cited several examples of such injection solutions, as well as support from Dr. Nelson for that proposition. *Id.* (citing the pH ranges of various solutions: 4.5-7.0 for sodium chloride (citing A595-96); 3.5-6.5 for dextrose (citing A594); 5.7 for 0.9% saline (citing A597-611), and 4.5 for 5% dextrose (citing A612-623)); A163-164 (Nelson Decl. ¶¶ 94-95). The Board ignored this argument completely.

The Board's repeated focus on epimerization improperly elevated a single motivation to the exclusion of other motivations. Such an analysis is precisely the "narrow conception" eliminated by the Supreme Court in *KSR*. 550 U.S. at 419. Had the Board considered other motivations, it would have found Claims 1-23 obvious.

CONCLUSION

The Board made two legal errors in this case: (1) improperly importing an epimeric stability limitation into the composition claims at issue in violation of *Senju* and (2) failing to consider motivations to substitute or combine references beyond the problem the patentee was trying to solve in violation of *KSR* and its progeny. The first error caused the Board to disregard CN '550 and Pawelczyk, which together with Naggar would have rendered Claims 1-23 invalid. The second error allowed the Board to disregard several key motivations, each of which provides a basis for a conclusion of obviousness. Based on these fundamental errors, this Court should reverse and/or vacate the Board's judgment of non-obviousness and remand the case to the Board for a proper consideration of Apotex's asserted references and arguments.

Dated: October 29, 2015

Respectfully submitted,

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ADDENDUM

ADDENDUM

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571-272-7822

Paper 94
Date: April 20, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner,

v.

WYETH LLC,
Patent Owner.

Case IPR2014-00115
Patent 7,879,828 B2

Before FRANCISCO C. PRATS, JACQUELINE WRIGHT BONILLA, and JO-ANNE M. KOKOSKI, *Administrative Patent Judges.*

KOKOSKI, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Apotex Inc. ("Petitioner") filed a Petition (Paper 1, "Pet.") to institute an *inter partes* review of claims 1–23 of U.S. Patent No. 7,879,828 B2 (Ex. 1001, "the '828 patent"). Wyeth LLC ("Patent Owner") did not file a preliminary response. We determined that the information presented in the Petition demonstrated that there was a reasonable likelihood that Petitioner would prevail in challenging claims 1–23 as unpatentable under 35 U.S.C. § 103 as obvious over the combination of CN '550,[1] Pawelczyk,[2] and Naggar.[3] Pursuant to 35 U.S.C. § 314, we instituted this proceeding on April 21, 2014. Paper 10 ("Dec. to Inst."), 2, 9.

Patent Owner filed a Patent Owner Response (Paper 36, "PO Resp."), and Petitioner filed a Reply (Paper 60, "Reply"). Petitioner filed a Motion to Exclude (Paper 62) portions of the Declarations of Dr. Henry Grabowski (Ex. 2010) and Mr. Christian L. Ofslager (Ex. 2011), as well as a number of Patent Owner's other exhibits. Patent Owner filed an Opposition to the Motion to Exclude (Paper 73), and Petitioner filed a Reply (Paper 75). Patent Owner filed a Motion to Exclude (Paper 66) CN '550 and its accompanying translations and declarations (Exs. 1003–1005, 1046, 1047), and portions of the cross examinations of Dr. Lester Mitscher (Ex. 2175) and

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[1] Chinese Patent Publication No. CN 1390550A, published January 15, 2003 (Ex. 1003 and Exs. 1004 and 1046 (English translations)).

[2] E. Pawelczyk et al., *Kinetics of Drug Decomposition. Part 74. Kinetics of Degradation of Minocycline in Aqueous Solution*, 34 POL. J. PHARMACOL. PHARMA. 409–421 (1982) (Ex. 1006).

[3] V. Naggar et al., *Effect of Solubilizers on the Stability of Tetracycline*, 29(2) PHARMAZIE 126–129 (1974) (Ex. 1007).

Dr. Robert Williams (Ex. 2176). Petitioner filed an Opposition (Paper 70), and Patent Owner filed a Reply (Paper 76).

Petitioner supports its Petition with a Declaration by Mark L. Nelson, Ph.D. (Ex. 1002, "Nelson Decl."). Patent Owner relies on Declarations by Lester A. Mitscher, Ph.D. (Ex. 2008, "Mitscher Decl."), Robert O. Williams III, Ph.D. (Ex. 2009, "Williams Decl."), Harry Grabowski, Ph.D. (Ex. 2010, "Grabowski Decl."), and Christian L. Ofslager (Ex. 2011, "Ofslager Decl.").

An oral hearing was held on January 23, 2015. A transcript of the hearing is included in the record. Paper 89 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons that follow, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–23 of the '828 patent are unpatentable.

A. The '828 Patent

The '828 patent relates generally to compositions comprising tigecycline, a suitable carbohydrate, and an acid or buffer. Ex. 1001, 1:8–12. Tigecycline, a chemical analog of minocycline, is a tetracycline antibiotic used to treat drug-resistant bacteria. *Id.* at 1:22–25. Due to poor oral bioavailability, tigecycline typically is formulated as an intravenous solution that is prepared from a lyophilized tigecycline powder immediately prior to administration. *Id.* at 1:45–50. In solution, tigecycline undergoes oxidation at slightly basic pH, causing the tigecycline to degrade relatively rapidly. *Id.* at 2:24–26, 33–40. When the pH of the solution is lowered, however, oxidative degradation decreases, and degradation by epimerization predominates. *Id.* at 2:43–49. The tigecycline epimer lacks antibacterial

effect, and is, thus, an undesirable degradation product. *Id.* at 3:19–22. According to the '828 patent, the claimed compositions reduce tigecycline degradation, because the acidic pH of the solution comprising tigecycline and a suitable carbohydrate minimizes oxidative degradation, while the carbohydrate stabilizes the tigecycline against epimerization in the acidic solution. *Id.* at 4:49–59.

The Specification of the '828 patent discloses various embodiments, such as compositions comprising tigecycline, lactose, and hydrochloric acid, at pH values between 3.0 and 7.0. *Id.* at 7:63–10:35, 11:15–12:53. The Specification further discloses embodiments where the molar ratio of tigecycline to lactose varies between 1:0.24 and 1:4.87. *Id.* at 13:40–14:33.

Claims 1 and 12 of the '828 patent are independent. Claims 2–11 depend, directly or indirectly, from claim 1, which is reproduced below:

> 1. A composition comprising tigecycline, lactose, and an acid selected from hydrochloric acid and gentisic acid, wherein the molar ratio of tigecycline to lactose is between about 1:0.2 and about 1:5 and the pH of the composition in a solution is between about 3.0 and about 7.0.

Id. at 14:36–40.

Claims 13–23 depend, directly or indirectly, from claim 12, which is reproduced below:

> 12. A composition comprising tigecycline, lactose, and hydrochloric acid, wherein the molar ratio of tigecycline to lactose is between about 1:0.2 and about 1:5 and the pH of the composition in a solution is between about 3.0 and about 7.0.

Id. at 14:62–65.

II. ANALYSIS

A. Claim Interpretation

In an *inter partes* review, "[a] claim in an unexpired patent shall be given its broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC.*, 778 F.3d 1271, 1279–80 (Fed. Cir. 2015). Under this standard, claim terms are given their ordinary and customary meaning in view of the specification, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

For purposes of our Decision to Institute, we determined that the terms in the challenged claims did not need to be construed expressly, and we see no reason to modify that determination in light of the record developed at trial.

B. Obviousness of Claims 1–23 over CN '550, Pawelczyk, and Naggar

To prevail on its patentability challenge, Petitioner must establish facts supporting its challenge by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). We instituted review based upon Petitioner's contention that the combination of CN '550, Pawelczyk, and Naggar rendered claims 1–23 obvious under 35 U.S.C. § 103. Upon consideration of the parties' arguments and evidence before us now, we determine that Petitioner has not demonstrated by a preponderance of the evidence that those claims would have been obvious over the combination of CN '550, Pawelczyk, and Naggar for the reasons explained below.

1. Overview of CN '550

CN '550 is a Chinese-language patent application. Ex. 1003. In support of the Petition, Petitioner relied on a certified English translation of CN '550 (Ex. 1004,[4] "the first translation") that described lactose, and other ingredients, as excipients. *See, e.g.*, Ex. 1004, 1:32–33 ("[The formulation] is made of minocycline hydrochloride, an excipient, and a pH adjusting agent."), 3:35–37 ("The excipient is . . . selected from mannitol, glucose, NaCl, dextran, lactose, and hydrolyzed gelatin."); Pet. 26–30. After the Decision to Institute issued, but before the Patent Owner Response was filed, Patent Owner objected to the first translation on the basis that "excipient" should have been translated as "lyophilized powder supporting agent," and that lactose was included in a list of excipients on page 3 of the translation, when it did not appear in the original text. Transcript of Teleconference, Ex. 2172, 16:6–22; Paper 66, 3.

In response to Patent Owner's objections, Petitioner submitted a corrected certified translation of CN '550 (Ex. 1046,[5] "the corrected translation"). In the corrected translation, the characters originally translated as "excipient" are translated as "lyophilized powder supporting agent," and lactose no longer appears in the list on page 3. *See, e.g.*, Ex. 1046, 1 ("[The formulation] is made of minocycline hydrochloride, a lyophilized powder supporting agent, and a pH adjusting agent."), 3 ("The lyophilized powder supporting agent is . . . selected from mannitol, glucose, NaCl, dextran, and

[4] The cited page numbers in Exhibit 1004 refer to the numbers at the bottom of each page, rather than those at the top.
[5] The cited page numbers in Exhibit 1046 refer to the numbers at the bottom of each page, rather than those at the top.

hydrolyzed gelatin."). Patent Owner does not object to the content of the corrected translation, but did file a motion to exclude both translations, which we address below. Ex. 2172, 28:5–15; Paper 66, 1–13.

Although we relied upon the first translation in the Decision to Institute, we rely on the corrected translation in rendering this Final Decision. As such, the following discussion of CN '550 with respect to Petitioner's contention that the '828 patent would have been obvious over the combination of CN '550, Pawelczyk, and Naggar is based on the corrected translation.

CN '550 is directed to lyophilized minocycline hydrochloride powder injections. Ex. 1046, 1. The lyophilized powder is comprised of 0.05–10 parts (by weight) minocycline hydrochloride, 0–100 parts lyophilized powder supporting agent, and a suitable amount of a pH adjusting agent. *Id.* at 3. The lyophilized powder supporting agent can be selected from mannitol, glucose, sodium chloride, dextran, lactose, and hydrolyzed gelatin. *Id.* at 2 (claim 5), 3. The pH adjusting agent is an inorganic acid, such as hydrochloric acid. *Id.* at 3. The pH of the lyophilized powder is 0–7.5, most preferably 2–3.5. *Id.* CN '550 discloses an embodiment in Example 1 that contains 108 g minocycline hydrochloride, 210 g mannitol, and a suitable amount of 0.1 M hydrochloric acid. *Id.* at 4. Example 2 discloses an embodiment containing 108 g of minocycline hydrochloride, 210 g of dextran, and a suitable amount of acetic acid. *Id.* Example 3 describes an embodiment containing 108 g minocycline hydrochloride, 210 g hydrolyzed gelatin, and a suitable amount of phosphoric acid. *Id.* at 5.

2. Overview of Pawelczyk

Pawelczyk reports the results of studies investigating the stability of minocycline in aqueous solutions over a broad pH range. Ex. 1006, 409. Pawelczyk discloses aqueous minocycline solutions at pH 4.38, 4.86, and 5.42. *Id.* at 413, Table 1. Pawelczyk teaches that oxidation is the predominant minocycline degradation process above pH 5. *Id*. at 417.

3. Overview of Naggar

Naggar details an investigation of the rate of tetracycline epimerization under various experimental conditions. Ex. 1007, 126. Naggar teaches that, at a pH of 2–6, tetracycline undergoes a reversible epimerization at the C4 dimethylamino group. *Id.* The epimerization occurs most rapidly at a pH of 3–4. *Id.* Naggar teaches that solubilizers (such as polysorbate 20, PEG 6000, urea, and thiourea) interact with tetracycline and act as deprotonating agents, thus inhibiting epimerization by deterring the rearrangement of tetracycline ring A. *Id.* at 127. Naggar reports that tetracycline and a solubilizer in solution with a pH of 3–5 is "chemically stable over a long period of time." *Id.*

4. Analysis

Petitioner contends that CN '550 discloses a lyophilized composition that is stabilized against light, heat, oxygen, and water, and contains (1) minocycline (an analog of tigecycline), (2) lactose, glucose, or dextran, and (3) hydrochloric acid. Pet. 31–40. Petitioner contends that a person skilled in the art "would find reason to substitute tigecycline for minocycline in the lyophilized formulation of CN '550" because tigecycline was known to work where other antibiotics, including other tetracyclines had failed, and because minocycline and tigecycline are tetracycline antibiotics that have

identical A and B rings, and undergo epimerization at the C4 dimethylamino group by the same reaction. *Id.* at 31–32. Petitioner also contends that because Naggar teaches that tetracyclines are stabilized against epimerization by hydrogen bonding between a saccharide (such as lactose) and a tetracycline, "a person of ordinary skill in the art would understand and expect that lactose disclosed in CN '550 would also be effective to stabilize tigecycline against epimerization." *Id.* at 44.

Patent Owner asserts that CN '550 does not teach or suggest the use of lactose to minimize or prevent epimerization. PO Resp. 24–27. Patent Owner asserts that CN '550 describes lactose as a "lyophilized powder supporting agent," which "provides physical support to a lyophilized powder formulation" so that it does not collapse, not as "an ingredient that engages in chemical interactions such as deprotonating the active ingredient to avoid epimerization." *Id.* at 24. Therefore, according to Patent Owner, a person having ordinary skill in the art would have understood that lyophilized powder supporting agents "play a very specific role in maintaining physical structure," and "would never have looked" at the disclosure of lactose in CN '550 to enhance chemical stability of a tigecycline formulation. *Id.* at 26. Patent Owner notes that other lyophilized powder supporting agents named in CN '550, such as mannitol, sodium chloride, and hydrolyzed gelatin, do not "suggest a common chemical interaction or bonding potential" or have similar structures that would suggest, to a person having ordinary skill in the art, a common interaction between each named lyophilized powder supporting agent and a tetracycline derivative. *Id.* at 25. Patent Owner also asserts that there is no indication, in any event, that the compositions described in CN '550 were epimerically stable. *Id.* at 28–30.

Patent Owner further asserts that Naggar does not teach an ordinary artisan that lactose can be used to stabilize tetracyclines against epimerization. PO Resp. 31–36. Patent Owner notes that Naggar does not disclose lactose, and the disclosed compound noted by Petitioner—polysorbate 20—is not as effective against epimerization as other disclosed solubilizers, such as PEG 6000 and thiourea. *Id.* at 31–32. There is therefore no reason, Patent Owner asserts, for a person having ordinary skill in the art to choose lactose to stabilize tigecycline against epimerization based on the disclosures in Naggar. *Id.* at 32–36.

We agree with Patent Owner that Petitioner has not shown, by a preponderance of the evidence, that a person having ordinary skill in the art would have had reason to substitute tigecycline for minocycline in the lyophilized formulation of CN ’550, or to make the compositions recited in the challenged claims in particular in any event. Pet. 31–33. As discussed in more detail below, none of CN ’550, Pawelczyk, or Naggar discloses or discusses tigecycline. PO Resp. 19. Petitioner does not explain adequately why an ordinary artisan, reading such references, would have had reason to use tigecycline in the formulation of CN ’550 when the references themselves lack any teaching or suggestion about the use or specific chemistry of tigecycline in particular. In addition, we also agree with Patent Owner that Petitioner has not shown sufficiently that a person having ordinary skill in the art would have considered it obvious to include lactose in a tigecycline composition in the amounts recited in the ’828 patent claims, for example, to stabilize the composition against epimerization.

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the subject matter sought to be patented and the prior art are such

that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). Prior art references must be "considered together with the knowledge of one of ordinary skill in the pertinent art." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Moreover, an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418. A patent claim composed of several elements is not proved obvious merely by demonstrating that each of its elements was known, independently, in the prior art. *Id.* A party that petitions the Board for a determination of obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)).

a. Substituting Tigecycline for Minocycline

Petitioner states that a person of ordinary skill in the art would have found reason to substitute tigecycline for minocycline in the CN '550 compositions because it was known to work where other antibiotics failed, and that it was active against specific viruses that show tetracycline resistance. Pet. 31. Petitioner cites Dr. Nelson's testimony in support of this contention:

> A person of ordinary skill in the art in 2005 would find reason to substitute tigecycline for minocycline in the lyophilized formulation of CN '550, because the '828 Patent states that it was known that tigecycline "has been shown to work where other antibiotics have failed" and "it has been active against methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae*, vancomycin resistant enterococci…and against organisms carrying either of the two major forms of tetracycline resistance: efflux and ribosomal protection."

Nelson Decl., Ex. 1002 ¶ 84 (citing Ex. 1001, 1:23–44).

Dr. Nelson does not explain, however, why the knowledge that tigecycline is effective "where other antibiotics have failed" would lead a person having ordinary skill in the art to substitute tigecycline for minocycline in the CN '550 compositions. Neither Petitioner nor Dr. Nelson provides information demonstrating that a person of ordinary skill in the art would correlate the therapeutic effectiveness of tigecycline as an antibiotic to the properties of tigecycline that must be considered when preparing a lyophilized formulation of tigecycline. Moreover, Petitioner does not provide any evidence or explanation why a person having ordinary skill in the art would have expected reasonably that the substitution tigecycline for minocycline in the CN '550 compositions would have resulted in a stabilized tigecycline composition. Petitioner, therefore, has not provided sufficient rationale to explain why a person having ordinary skill in the art would have substituted tigecycline for minocycline in the CN '550 compositions for any reason, much less in an attempt to make a lyophilized tigecycline composition that was stable against epimerization on this basis, as Petitioner contends.

Petitioner also argues that a person having ordinary skill in the art "would understand and expect that lactose would be effective to stabilize minocycline and tigecycline against C4 epimerization in a solution having a pH from 0.1–7.5, including an acid pH of 2.0–3.5, as taught by CN '550, based on the exact structural identity of the A and B rings in these analogs." Pet. 32 (citing Nelson Decl., Ex. 1002 ¶ 88). Petitioner goes on to conclude:

> A person of ordinary skill in the art would expect each of the saccharide excipients disclosed in CN '550 to be effective to stabilize minocycline and tigecycline against C4 epimerization in a solution having a pH from 0.1–7.5, including an acid pH of 2.0–3.5, because of the structural similarities of glucose (a monosaccharide), lactose (a disaccharide), and dextran (a polysaccharide). It was known in the prior art, including CN '550, that suitable carbohydrates including disaccharides such as lactose, monosaccharides such as glucose, and polysaccharides such as dextran, are effective to stabilize tetracyclines against epimerization at acid pHs.

Id. (citing Nelson Decl., Ex. 1002 ¶¶ 42–50, 56–59, 86–87).

Petitioner's contentions in this regard are insufficient because they presume that a person of ordinary skill in the art would have recognized that the compositions disclosed in CN '550 were stable against epimerization. As is discussed below, Petitioner has not established that a person of ordinary skill in the art would have known from the CN '550 disclosure that the described minocycline compositions were stable against epimerization.

In its Reply, Petitioner argues that whether a person having ordinary skill in the art would have recognized that the CN '550 compositions were epimerically stable is irrelevant to the obviousness inquiry:

> Contrary to [Patent Owner]'s fundamental argument, the '828 patent claims do not relate to a method for stabilizing tigecycline against epimerization, or indeed, any method of stabilizing tigecycline. The claims recite a lyophilized

> ***composition***, containing tigecycline, lactose and hydrochloric acid, having a specified pH "in a solution" that is not limited to any one of the 3 solutions that are disclosed in the specification. The issue is whether a [person having ordinary skill in the art] would have found it obvious to make the claimed composition, by substituting tigecycline for minocycline in the composition disclosed in CN '550, for ***any*** reason, not just to reduce epimerization.

Reply 3 (citations omitted).

Petitioner also argues that a person having ordinary skill in the art would have expected, from CN '550's disclosure of minocycline compositions that are stabilized against degradation by light, heat, oxygen, and water that also have good therapeutic effectiveness, that similar benefits would result if tigecycline were simply substituted for minocycline. *Id.* at 4; *see also* Pet. 39 ("[a] person of ordinary skill in the art would recognize that the technique for stabilizing minocycline disclosed in CN '550 by using lactose, would similarly stabilize and improve a composition containing the analog antibiotic tigecycline"). As noted above, however, Petitioner does not establish adequately that an ordinary artisan would have had reason to believe that tigecycline, rather than minocycline, would have been similarly stable in the formulation disclosed in CN '550.

Petitioner is correct that the claims do not recite epimeric stability and therefore obviousness of the claims can be demonstrated without a showing of epimeric stability in the prior art. We are not persuaded, however, that Petitioner has established that a person having ordinary skill in the art would have found it obvious to substitute tigecycline for minocycline in the composition disclosed in CN '550.

b. Using Lactose to Stabilize a Lyophilized Tigecycline Composition

Petitioner relies on CN '550's disclosure of "stable" minocycline compositions as motivation for a person having ordinary skill in the art to combine CN '550 with Pawelczyk and Naggar to address the problem of tigecycline's instability due to epimerization. Pet. 40. In urging that a person having ordinary skill in the art would have used lactose to stabilize a lyophilized tigecycline composition against epimerization, Petitioner also points to Naggar's teaching that (1) tetracycline antibiotics undergo epimerization at pH conditions between 2 and 6, (2) the epimerization occurs at the C4 dimethylamino group, and (3) polysorbate 20 stabilizes tetracycline against epimerization. Pet. 42–44. Based on these disclosures in CN '550 and Naggar, and Pawelczyk's teaching that "a pH range below 5 is preferable to avoid oxidative degradation of minocycline," Petitioner concludes that "a person of ordinary skill in the art would understand and expect that lactose disclosed in CN '550 would also be effective to stabilize tigecycline against epimerization in solutions having a pH in the range from 4 to 6 taught as optimal by Naggar." *Id.* at 41, 44.

As Patent Owner points out, however, neither CN '550, Pawelczyk, nor Naggar discloses tigecycline, Naggar and Pawelczyk do not disclose lactose, and CN '550 only discloses lactose as one of a list of lyophilized powder supporting agents in a dependent claim. PO Resp. 19–20. In addition, although CN '550 states that the disclosed formulations are stable against light, heat, oxygen, and water (Ex. 1046, 1, 3), there are no statements from which a person skilled in the art would understand that the CN '550 formulations were epimerically stable. PO Resp. 23–24. Indeed,

neither CN ’550 nor Pawelczyk mention epimerization at all. As discussed above, the ’828 patent, but none of the cited prior art references, discloses that compositions having the claimed ingredients and pH are stabilized against oxidative degradation and epimerization of tigecycline.

In support of its contention regarding the epimeric stability of the compositions disclosed in CN ’550, Petitioner relies on Dr. Nelson’s testimony in which he asserts that “CN ’550 discloses that the lyophilized powder is stabilized under acidic conditions, and a person of ordinary skill in the art would readily appreciate that stabilization would include prevention of C4 epimerization in an acidic solution by the disclosed excipients, which include the carbohydrates lactose, glucose and dextran.” Nelson Decl., Ex. 1002 ¶ 78. Dr. Nelson concedes that CN ’550 does not mention epimerization explicitly (Complete Deposition Transcript of Mark L. Nelson, Ph.D., Ex. 2012, 38:6–39:15), but argues that a person skilled in the art would understand that because epimerization affects stability, and CN ’550 discloses stable formulations, those formulations must be epimerically stable. *Id.* at 47:11–23.

Dr. Nelson’s statements regarding what a person skilled in the art would have understood about the epimeric stability of the CN ’550 compositions, however, are not supported by any objective evidence or analysis. Dr. Nelson simply states the skilled artisan would “readily appreciate” that the CN ’550 compositions are epimerically stable, without providing any explanation as to why that would be the case. Dr. Nelson relies on CN ’550’s teaching that the disclosed compositions feature stable light, thermal, oxygen, and water properties, but does not expound upon the reasons why a person skilled in the art would understand that statement to

include epimeric stability. *See, e.g.,* Nelson Decl., Ex. 1002 ¶ 78. Dr. Nelson's unsupported and unexplained opinions are not persuasive. *See* 37 C.F.R. § 42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight."); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) (stating a lack of objective support for an expert opinion "may render the testimony of little probative value in [a patentability] determination").

Patent Owner, in contrast, provides reasoning as to why a person having ordinary skill in the art would not have understood CN '550 to address epimeric stability. PO Resp. 22–24. For example, Patent Owner notes that CN '550 does not include data, studies, or any explicit indication that epimeric stability was a part of the disclosure. *Id.* at 23; *see also* Williams Decl., Ex. 2009 ¶ 69 ("A [person of ordinary skill in the art] simply would not believe that a reference solves an epimerization problem if it neither mentions epimerization, nor provides any analytical data relating to epimerization."). Dr. Mitscher also testified that a person having ordinary skill in the art would not understand that the compositions described in CN '550 reduced epimerization:

> Nor does the bare statement that CN '550 that the goal of the study was "to provide a lyophilized minocycline hydrochloride powder injection that features stable light, thermal, oxygen, and water properties; is non-polluting and easy to manipulate, transport, and store" teach or suggest that the formulations reduced epimerization. To the contrary, if the invention were targeted at preventing epimerization as well, a [person of ordinary skill in the art] would have expected epimerization to be included in this list or otherwise mentioned. The fact that it is absent would lead a [person of ordinary skill

> in the art] to believe that either the formulations do not work to solve an epimerization problem, or that the authors did not test or otherwise have reason to believe that the disclosed formulations were solutions to the epimerization problem.

Mitscher Decl., Ex. 2008 ¶ 110 (internal citations omitted). We find Patent Owner's arguments, that a person having ordinary skill in the art would not have looked to a reference that does not mention epimerization in order to solve the problem of epimeric instability of tigecycline compositions, to be persuasive. PO Resp. 22–24; *see Yorkey v. Diab*, 601 F.3d 1279, 1284 (Fed. Cir. 2010) (holding that Board has discretion to give weight to one item of evidence over another "unless no reasonable trier of fact could have done so").

Dr. Nelson also relies on the following statement in CN '550 regarding the therapeutic effectiveness of the disclosed lyophilized minocycline compositions as further support of Petitioner's contention that the disclosed lyophilized powder supporting agents are stabilizing the formulations against epimerization (Ex. 2012, 91:3–93:16; PO Resp. 26–27):

> This disclosure is a lyophilized powder for injection with a pH level of 0–7.5, with the most suitable level being 2–3.5. Its uses are as follows: It has a very good therapeutic effect on a variety of infections caused by drug-resistant Staphylococcus aureus, Chlamydia, and Acinetobacter, and can be administered extravascularly. The lyophilized powder supporting agent is a soluble support easily dissolved in water and fast-dissolving in clinical applications, selected from mannitol, glucose, NaCl, dextran, and hydrolyzed gelatin.

Ex. 1046, 3.

Dr. Nelson does not provide any objective evidence explaining how the stated therapeutic effectiveness of the compositions in CN '550 correlates to epimeric stability. The mere fact that the CN '550

compositions are therapeutically effective does not necessarily mean that they are stable against epimerization. Patent Owner, however, provides evidence that stability testing does not correlate to the activity of a compound, which is determined using different testing methods. PO Resp. 29. Dr. Mitscher testified that "*stability* testing is distinct from the test of the *activity* of a compound, typically performed by assessing the minimum inhibitory concentration ('MIC') at which a compound inhibits growth of bacteria," and that "an MIC test is not intended to convey information regarding a compound's stability and does not do so." Mitscher Decl., Ex. 2008 ¶ 65 (emphasis in original).

Dr. Mitscher also explained that a person of ordinary skill in the art would not have relied on MIC testing to reach a conclusion about the degree of a compound's stability for a number of reasons, including that (1) MIC testing is performed on the active pharmaceutical ingredient, not on the formulation, and (2) there is no standard or accepted way of substituting MIC test results for stability test results. *Id.* ¶ 123. Dr. Williams agrees with Dr. Mitscher, and points out that a person of ordinary skill in the art "in 2005 would not have interpreted a statement about microbiological activity as indicative of the stability of a formulation, particularly a statement involving an active ingredient in the tetracycline class that is known to be susceptible to degradation." Williams Decl., Ex. 2009 ¶ 39.

Moreover, Dr. Nelson's testimony regarding the therapeutic effectiveness of the CN '550 compositions and the ability of lactose to stabilize minocycline against epimerization is based on an admittedly incorrect translation of CN '550. PO Resp. 25. Dr. Nelson's reliance on the statement of therapeutic effectiveness in CN '550 was premised on the first

translation's erroneous inclusion of lactose in the sentence "[t]he lyophilized powder supporting agent is a soluble support easily dissolved in water and fast-dissolving in clinical applications, selected from mannitol, glucose, NaCl, dextran, and hydrolyzed gelatin" that immediately followed the sentence describing therapeutic effectiveness. *Id.* at 26–27. According to Dr. Nelson, it was important that lactose appeared in the same paragraph as the statement of therapeutic effectiveness of the disclosed embodiments because "I would try the same experiment, just supplanting lactose for hydrolyzed gelatin because they'd mentioned that it works the same as the hydrolyzed gelatin." Ex. 2012, 91:3–25. Dr. Nelson further testified that this disclosure would provide motivation for a person skilled in the art to use lactose. *Id.* at 93:5–16. Although Dr. Nelson also testified that his conclusions are not changed by the corrected translation, neither he nor Petitioner provide any analysis or evidence as to why this is the case. *Id.* at 426:17–23.

Additionally, to the extent that Petitioner argues that a person having ordinary skill in the art would have been motivated to combine CN '550, Pawelczyk, and Naggar because they each teach stabilization of tetracyclines by saccharides (Tr. 31:4–7), that argument is similarly unpersuasive.

Specifically, Petitioner argues that Naggar's disclosure of the saccharide polysorbate 20 as being effective to stabilize tetracycline against epimerization "informs a person skilled in the art that the stabilization of tetracyclines including minocycline and tigecycline by saccharides involves a hydrogen bond between an excipient such as lactose and a tetracycline such as minocycline or tigecycline that may result from hydrogen bonding." Pet. 44. Dr. Nelson then explains that "polysorbate is a carbohydrate based

polymer having primary and secondary hydroxyl groups that are characteristic of saccharides," and further describes that "[c]arbohydrates including monosaccharides such as glucose and mannose; disaccharides exemplified by lactose and sucrose; and poly-saccharides such as dextran, have the ability" to stabilize epimerization "via an intramolecular interaction." Nelson Decl., Ex. 1002 ¶¶ 43, 45. At no point does Dr. Nelson or Petitioner explain adequately, however, why a person having ordinary skill in the art would have focused on Naggar's disclosure of polysorbate 20 over other solubilizers disclosed therein (when Naggar indicates that other solubilizers worked better), nor why one would have used lactose instead of polysorbate 20 in any event, when the reference does not mention other polysaccharides, much less lactose in particular.

Dr. Nelson's testimony is unpersuasive. Dr. Nelson opines that all of the elements of the claims disparately existed in the prior art, but fails to provide sufficient reason why one of ordinary skill in the art at the time of filing would have combined the different elements, some disclosed and some not, in the different references. *See, e.g., InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1348–49 (Fed. Cir. 2014) (holding expert testimony to be impermissible hindsight for failing to explain what reason or motivation one of ordinary skill in the art at the time of the invention would have had to place the prior art together).

In an obviousness determination, we must avoid analyzing the prior art through the prism of hindsight. Instead, we must "cast the mind back to the time the invention was made" and "occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." *W.L. Gore & Assoc., Inc. v. Garlock,*

Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983). Here, Petitioner attempts to imbue one of ordinary skill in the art with knowledge of the claimed invention, when no prior art reference or references of record conveys or suggests that knowledge. Rather, Petitioner's argument that CN '550 is combinable with Pawelczyk and Naggar appears to be premised on Petitioner's knowledge of the '828 patent's disclosure of lyophilized compositions of tigecycline and lactose that are stable against epimerization. *See*, *e.g.*, Tr. 28:6–12 ("The same saccharides are disclosed in the claims of the Chinese '550 patent . . . . The '828 patent says all disaccharides are expected to work. Saccharides are generally expected to work. And here are three that are expected to work. One of them is lactose, one of them is glucose, and one of them is dextran.").

c. Conclusion

Petitioner bears the burden of showing by a preponderance of the evidence that an ordinary artisan would have had reason to combine elements in the asserted prior art references to achieve the recited compositions. On the record before us, we find that Petitioner has not shown that the combination of CN '550, Pawelczyk, and Naggar renders the challenged claims unpatentable. Therefore, we conclude Petitioner has not demonstrated by a preponderance of the evidence that claims 1–23 of the '828 patent would have been obvious over the combination of CN '550, Pawelczyk, and Naggar.

C. Secondary Considerations of Non-Obviousness

Patent Owner contends that Petitioner fails to meet its burden of showing unpatentability because objective indicia of nonobviousness indicate that the claimed subject matter would not have been obvious. PO

Resp. 57–60. As discussed above, we find that Petitioner has not demonstrated that claims 1–23 would have been obvious over the combination of CN '550, Pawelczyk, and Naggar. Thus, we need not address Patent Owner's evidence regarding secondary considerations of nonobviousness.

III. MOTIONS TO EXCLUDE

A. Petitioner's Motion to Exclude

Petitioner moves to exclude Exhibits 2010 (Grabowski Declaration), 2011 (Ofslager Declaration), 2026, 2037–2151, and 2153–2168. Paper 62, 1, 4, 5, 8, 11. Because our Decision does not rely on any of the challenged exhibits, we dismiss Petitioner's Motion to Exclude as moot.

B. Patent Owner's Motion to Exclude

Patent Owner moves to exclude CN '550 and its accompanying translations and declarations (Exs. 1003–1005, 1046, 1047), and portions of the cross examinations of Dr. Mitscher and Dr. Williams (Exs. 2175, 2176). Paper 66, 1.

1. Exhibits 1004, 1005, 2175, and 2176

Because we do not rely on Exhibits 1004, 1005, nor Dr. Mitscher's or Dr. William's testimony on cross-examination in reaching the Final Written Decision, we dismiss as moot Patent Owner's Motion to Exclude as to Exhibits 1004, 1005, 2175, and 2176.

2. Exhibits 1003, 1046, and 1047

Patent Owner argues that Exhibit 1047 (Declaration of Jennifer Brooks filed in support of the corrected translation of CN '550 (Ex. 1046)) includes materially inaccurate statements regarding the errors in the first translation of CN '550 (Ex. 1004). Paper 66, 11–13. According to Patent

Owner, the declaration cannot support the corrected translation of CN '550 (Ex. 1046) because it does not comply with 37 C.F.R. § 42.63(b), and in the absence of a properly supported translation, CN '550 (Ex. 1003) is inadmissible. *Id.* at 13. Patent Owner does not object to the content of the corrected translation (Ex. 1046). *See* Paper 70, 1–2.

> Rule 42.63(b) states:
>
> When a party relies on a document or is required to produce a document in a language other than English, a translation of the document into English and an affidavit attesting to the accuracy of the translation must be filed with the document.

37 C.F.R. § 42.63(b); *see also* § 42.2 and §1.68 (defining "affidavit"). The Brooks Declaration (Ex. 1047) was signed by the translator of CN '550, states that the translation is true and accurate, and includes an acknowledgement that the statements are made of the declarant's own knowledge and with the "knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under section 1001 of Title 18 of the United States Code, and that such willful false statement may jeopardize the validity of the involved patent/application." Ex. 1047 ¶ 11. Therefore, Exhibit 1047 complies with § 42.63(b), and Exhibit 1046 is supported by a proper declaration.

Patent Owner further argues that the Brooks Declaration is misleading because it states that the inclusion of lactose in the first translation was an inadvertent error, and "that 'excipient' is merely a less literal translation, and there is no mention of the first declaration being submitted under Ms. Brooks' name without her knowledge or consent." Paper 66, 11–12. Patent Owner argues that Petitioner submitted the misleading declaration in order

to comply with Rule 42.123 regarding the filing of supplemental information. *Id.* at 10–11, 13.

Rule 42.123(b) states:

> A party seeking to submit supplemental information more than one month after the date the trial is instituted, must request authorization to file a motion to submit the information. The motion to submit supplemental information must show why the supplemental information reasonably could not have been obtained earlier, and that consideration of the supplemental information would be in the interests-of-justice.

37 C.F.R. § 42.123(b). According to Patent Owner, Petitioner could not show that the corrected translation could not have been obtained earlier without including the alleged misleading statements in the declaration. Paper 66, 13.

Here, the record reflects that Petitioner provided the corrected translation in response to Patent Owner's objections to the first translation, and that Patent Owner does not object to the translation itself. Patent Owner does not identify any reason why we would be unable to weigh this evidence without prejudice or confusion.

In addition, as the moving party, Patent Owner does not persuade us that Exhibit 1047 does not comply with § 42.63(b). Accordingly, we deny Patent Owner's Motion to Exclude in relation to Exhibits 1003, 1046, and 1047.

IV. CONCLUSION

For the reasons given, we are not persuaded that Petitioner has shown by a preponderance of the evidence that claims 1–23 of the '828 patent would have been obvious over the combined teachings of CN '550, Pawelczyk, and Naggar.

V. ORDER

In consideration of the foregoing, it is

ORDERED that Petitioner has not shown by a preponderance of the evidence that claims 1–23 of the '828 patent are unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude (Paper 62) is *dismissed*;

FURTHER ORDERED that Patent Owner's Motion to Exclude (Paper 66) is *dismissed-in-part* and *denied-in-part*; and

FURTHER ORDERED that because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2014-00115
Patent 7,879,828 B2

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(12) **United States Patent**
Fawzi et al.

(10) **Patent No.: US 7,879,828 B2**
(45) **Date of Patent: Feb. 1, 2011**

(54) **TIGECYCLINE COMPOSITIONS AND METHODS OF PREPARATION**

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(57) **ABSTRACT**

The present invention relates to novel tigecycline compositions with improved stability in both solid and solution states and processes for making these compositions. These compositions comprise tigecycline, a suitable carbohydrate, and an acid or buffer.

23 Claims, No Drawings

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TIGECYCLINE COMPOSITIONS AND METHODS OF PREPARATION

This application claims priority from provisional application Ser. No. 60/661,030 filed Mar. 14, 2005 the entire disclosure of which is hereby incorporated by reference.

The present invention relates to improved tigecycline compositions and methods for making such compositions. The inventive compositions have improved stability in both solid and solution states. The inventive compositions comprise tigecycline, a suitable carbohydrate, and an acid or buffer. The combination of the suitable carbohydrate and the acid or buffer reduces tigecycline degradation as explained below. The present invention provides advantages over the prior art by providing for stable tigecycline compositions and methods for making such compositions that achieve stability against both oxidative degradation and epimerization. These compositions are, therefore, more stable when dissolved, lyophilized, reconstituted, and/or diluted than compositions of tigecycline not made according to the invention.

Tigecycline is a known antibiotic in the tetracycline family and a chemical analog of minocycline. It may be used as a treatment against drug-resistant bacteria, and it has been shown to work where other antibiotics have failed. For example, it is active against methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant enterococci (D. J. Beidenbach et. al., Diagnostic Microbiology and Infectious Disease 40:173-177 (2001); H. W. Boucher et. al., Antimicrobial Agents & Chemotherapy 44:2225-2229 (2000); P. A. Bradford Clin. Microbiol. Newslett. 26:163-168 (2004); D. Milatovic et. al., Antimicrob. Agents Chemother. 47:400-404 (2003); R. Patel et. al., Diagnostic Microbiology and Infectious Disease 38:177-179 (2000); P. J. Petersen et. al., Antimicrob. Agents Chemother. 46:2595-2601 (2002); and P. J. Petersen et. al., Antimicrob. Agents Chemother. 43:738-744(1999), and against organisms carrying either of the two major forms of tetracycline resistance: efflux and ribosomal protection (C. Betriu et. al., Antimicrob. Agents Chemother. 48:323-325 (2004); T. Hirata et. al. Antimicrob. Agents Chemother. 48:2179-2184 (2004); and P. J. Petersen et. al., Antimicrob. Agents Chemother. 43:738-744(1999).

Tigecycline has historically been administered intravenously because it exhibits generally poor bioavailability when given orally. Intravenous solutions have largely been prepared immediately prior to use, e.g., administration to a patient, from lyophilized powders because tigecycline degrades in solution principally via oxidation. It would be preferable as well as desirable to have an intravenous formulation of tigecycline that did not require immediate use and could remain stable in solution for up to 24 hours.

Tigecycline is currently manufactured as a lyophilized powder. Due to the propensity for tigecycline to degrade, these powders are prepared under low-oxygen and low-temperature conditions in order to minimize degradation. Such processing is expensive because it requires special equipment and handling.

The typical process for preparing these powder compositions involves dissolving tigecycline in water (compounding) and lyophilizing (freeze-drying) the solution to dryness to form solid cakes of amorphous tigecycline. These cakes are then loaded under nitrogen into stoppered glass vials and shipped to end users such as hospital pharmacies. Prior to being administered to patients, the cakes are reconstituted,

often in 0.9% saline, to a concentration of, for example, about 10 mg/mL. At this concentration, tigecycline degrades rapidly in solution and therefore, must be used without delay. Thus, these reconstituted solutions are immediately diluted (also known as admixing) to about 1 mg/mL with saline or other pharmaceutically acceptable diluents into intravenous bags for patient delivery.

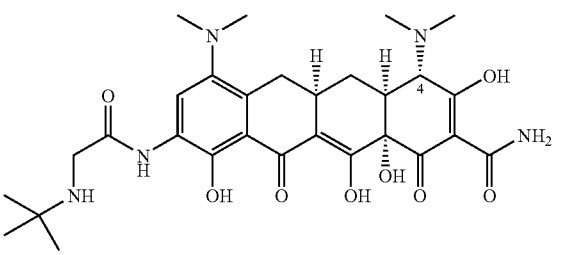
In this diluted state, tigecycline is ready for intravenous delivery to a patient. At a concentration of 1 mg/mL, however, tigecycline should be used within 6 hours of dilution. Because intravenous infusions may take several hours, hospital personnel must act quickly so that from the time admixture begins to the time the tigecycline dose has been administered to a patient, not more then 6 hours have elapsed. It would be more preferred to provide hospital staff with the flexibility and advantages that come with longer admixture and reconstitution times so that, for instance, a hospital pharmacist could prepare a solution the day before it is needed to be administered to a patient.

Tigecycline has such a short admixture time and the reconstitution time is essentially zero because in solution, tigecycline oxidation is relatively rapid. Under current manufacturing, storage, and administration conditions, the most prevalent form of degradation is via oxidation. The reason oxidation is the most prevalent form of degradation in previous formulations relates to the chemical structure of tigecycline. It possesses a phenol moiety, and it is well known in the art of organic chemistry that phenols are particularly prone to oxidation. When tigecycline is dissolved in water prior to lyophilization, the pH is slightly basic (about 7.8). This is higher than the pKa of the phenolic group on tigecycline. Thus, in both water and saline solutions, the phenolic group becomes deprotonated and more susceptible to reaction with oxygen which is why tigecycline compounding and lyophilization occur under a nitrogen blanket. Accordingly, care to avoid unnecessary exposure to oxygen must be taken by hospital staff during reconstitution and dilution.

If the pH of the tigecycline solution were less than the pKa of the phenolic group on tigecycline, then oxidation would occur, but to a lesser extent. Indeed, it has been observed that tigecycline oxidative degradation does decrease when the pH is lowered. At low pH, however, another degradative process occurs, epimerization. At lower pHs, epimerization emerges as the most predominant degradation pathway.

Tigecycline differs structurally from its epimer in only one respect.

FORMULA I



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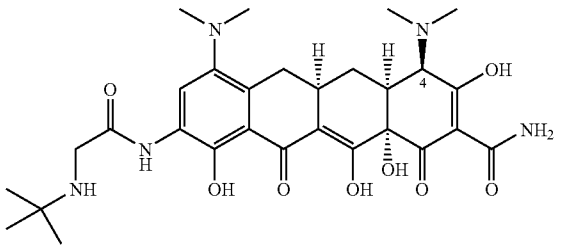
FORMULA II



In tigecycline, the N-dimethyl group at the 4 carbon is cis to the adjacent hydrogen as shown above in formula I, whereas in the epimer, formula II, they are trans to one another in the manner indicated. Although the tigecycline epimer is believed to be non-toxic, it lacks the antibacterial efficacy of tigecycline and is, therefore, an undesirable degradation product.

In the lyophilized state, tigecycline follows the same degradation pathways as in solution, but the rate of degradation is slower. Thus, when tigecycline is lyophilized in water such that the pH is about 7.8, the resulting lyophilized cake exhibits oxidative degradation, albeit at a slower rate than in solution. Similarly, when tigecycline is lyophilized in an acidic solution, the primary degradation pathway is epimerization and it also occurs at a slower rate than in solution.

Epimerization is a known degradation pathway in tetracyclines generally, although the rate of degradation may vary depending upon the tetracycline. Comparatively, the epimerization rate of tigecycline is particularly fast. The tetracycline literature reports several methods scientists have used to try and minimize epimer formation in tetracyclines. In some methods, the formation of calcium, magnesium, zinc or aluminum metal salts with tetracyclines limit epimer formation when done at basic pHs in non-aqueous solutions. (Gordon, P. N, Stephens Jr, C. R., Noseworthy, M. M., Teare, F. W., U.K. Patent No. 901,107). In other methods, (Tobkes, U.S. Pat. No. 4,038,315) the formation of a metal complex is performed at acidic pH and a stable solid form of the drug is subsequently prepared.

Other methods for reducing epimer formation include maintaining pHs of greater than about 6.0 during processing; avoiding contact with conjugates of weak acids such as formates, acetates, phosphates, or boronates; and avoiding contact with moisture including water-based solutions. With regard to moisture protection, Noseworthy and Spiegel (U.S. Pat. No. 3,026,248) and Nash and Haeger, (U.S. Pat. No. 3,219,529) have proposed formulating tetracycline analogs in non-aqueous vehicles to improve drug stability. However, most of the vehicles included in these inventions are more appropriate for topical than parenteral use. Tetracycline epimerization is also known to be temperature dependent so production and storage of tetracyclines at low temperatures can also reduce the rate of epimer formation (Yuen, P. H., Sokoloski, T. D., J. Pharm. Sci. 66:1648-1650,1977; Pawelczyk, E., Matlak, B, Pol. J. Pharmacol. Pharm. 34: 409-421, 1982). Several of these methods have been attempted with tigecycline but none have succeeded in reducing both epimer formation and oxidative degradation while not introducing additional degradants. Metal complexation, for example, was found to have little effect on either epimer formation or degradation generally at basic pH.

Although the use of phosphate, acetate, and citrate buffers improve solution state stability, they seem to accelerate degradation of tigecycline in the lyophilized state. Even without a buffer, however, epimerization is a more serious problem with tigecycline than with other tetracyclines such as minocycline.

Others of these methods similarly failed to reduce both epimerization and oxidative degradation. Although it was found that maintaining a pH of greater than about 6.0 helps reduce epimer formation, as noted above, such conditions lead to greater oxygen sensitivity. With respect to non-aqueous vehicles, although water is known to accelerate tigecycline degradation, it would be impractical to prepare an intravenous medication using such vehicles.

Whereas it has been determined that processing at temperatures lower than room temperature, such as below about 10° C., reduces the tigecycline degradation rate, such processing is expensive and it would be advantageous to use a composition that did not require expensive refrigeration during processing.

Chinese patent application CN 1390550A discloses that minocycline could be combined with an acid to increase the stability toward the oxidative degradation. It further discloses the use of a caking agent, such as mannitol. This reference says nothing about tigecycline nor does it suggest that carbohydrates could be used to reduce either oxidation or epimerization for minocycline in reduced pH environments. Indeed, minocycline can be formulated as a hydrochloride salt in intravenous products without significant epimerization. In tigecycline hydrochloride salts, however, significant epimerization occurs. Thus, minocycline and tigecycline possess different epimerization properties.

In another experiment, minocycline was lyophilized at a pH of about 5.0 and the lyophilized cake was stored for 20 days at 40° C. and 75% relative humidity. At the end of the 20 days, the cake was analyzed by HPLC. The epimer of minocycline was measured to be present at a level of 2.65% by mass. By comparison, when tigecycline was lyophilized at a pH of about 5.0 and the sample stored under the same conditions, but for only 4 days followed by HPLC analysis, the tigecycline epimer was measured to be at a level of 5.40%, over twice as much even though tigecycline was only stressed for $\frac{1}{5}^{th}$ as long as minocycline. Thus, tigecycline epimerizes much more readily than minocycline, and epimerization is a much more significant problem with tigecycline than it is for minocycline.

The present invention addresses the various problems and disadvantages of the prior art by providing for stable compositions of tigecycline in solid and solution form. By lyophilizing an aqueous solution containing tigecycline and a suitable carbohydrate at an acidic pH, we have prepared tigecycline compositions that are more stable against both oxidative degradation and epimerization than existing compositions. Because the pH is acidic, oxidative degradation has been minimized. Furthermore, it has been determined that suitable carbohydrates act to stabilize tigecycline against epimer formation at acidic pHs.

Compositions of the invention are more stable in the lyophilized state than the existing compositions and do not require low-temperature or low-oxygen processing conditions. Such compositions are also expected to possess reconstitution and admixture stability times greater than that of the existing compositions. For example, one embodiment of the invention is stable for 6 hours after reconstitution and stable for an additional 18 hours after admixture. These extended

stability times make tigecycline much easier to use in a hospital environment by providing needed flexibility to hospital staff when treating patients.

Solid-state compositions of the invention comprise tigecycline, a suitable carbohydrate, and an acid or buffer.

Suitable carbohydrates are those carbohydrates capable of reducing epimer formation in at least one solid form prepared in at least one pH environment when compared to a tigecycline solid form prepared at the same pH environment lacking suitable carbohydrates. In one embodiment, the pH environment ranges from about 3.0 to about 7.0, such as pHs ranging from about 4.0 to about 5.0, or from about 4.2 to about 4.8. In one embodiment, the at least one solid form is chosen from powders and lyophilized cakes of tigecycline. Examples of suitable carbohydrates include the anhydrous, hydrated, and solvated forms of compounds such as lactose, mannose, sucrose, and glucose. Suitable carbohydrates include mono and disaccharides e.g. an aldose monosaccharide or a disaccharide, preferably a disaccharide such as lactose and sucrose. Lactose is most preferred. Accordingly, suitable carbohydrates may include different solid forms. For example, by lactose we include the different solid forms of lactose such as anhydrous lactose, lactose monohydrate or any other hydrated or solvated form of lactose. Lactose and sucrose are disaccharides. It is therefore expected that disaccharides as a class will work according to the invention.

The compositions of the invention include solutions, such as those prepared prior to lyophilization, containing tigecycline, a suitable carbohydrate, and an acid or buffer. In some embodiments of the invention, the solutions may be stored for several hours prior to lyophilization in order to provide greater manufacturing flexibility. Compositions of the invention further include lyophilized powders or cakes containing tigecycline, a suitable carbohydrate, and an acid or buffer.

In some embodiments of the invention, the suitable carbohydrate used is lactose monohydrate and the molar ratio of tigecycline to lactose monohydrate in the lyophilized powder or cake is between about 1:0.2 to about 1:5. Some embodiments have tigecycline to lactose monohydrate molar ratios of between about 1:1.6 to about 1:3.3.

Compositions of the invention also include solutions made from the lyophilized powder or cake by, for example, reconstitution with saline or other pharmaceutically acceptable diluents. Compositions of the invention further include solutions resulting from diluting those reconstituted solutions with pharmaceutically acceptable diluents for use in intravenous bags.

Any carbohydrate capable of reducing epimer formation in the invention is a suitable carbohydrate and this invention is not limited to compositions employing those carbohydrates specifically identified.

It is expected that derivatives of sugars, for example, may work according to the invention to reduce epimer formation. Thus, to the extent that derivatives of sugars, such as sugar alcohols, glucoseamines, and alkyl esters alone or in combination reduce epimer formation according to the invention, they are suitable carbohydrates. Likewise, other suitable carbohydrates may include higher saccharides such as polysaccharides; complex carbohydrates such as hetastarch, dextran; and celluloses such as hydroxypropylmethyl cellulose and hydroxypropyl cellulose. It is further expected that combinations of carbohydrates, including monosaccharides and trisaccharides, will be suitable carbohydrates and work to reduce epimer formation according to the invention.

Acids and buffers of the invention include any pharmaceutically acceptable acid or buffer capable of adjusting the pH of a tigecycline/suitable carbohydrate solution to between about 3.0 to about 7.0, about 4.0 to about 5.0, or about 4.2 to about 4.8. Examples of such acids include, but are not limited to, hydrochloric acid, including 1.0 N HCl, gentisic acid, lactic acid, citric acid, acetic acid, and phosphoric acid. Examples of suitable buffers include succinates.

Compounds of the invention may be prepared via a number of acceptable methods. The methods described below are exemplary and not meant to limit the invention.

In one method of the invention, tigecycline is dissolved in water to form a solution. The pH of the solution is subsequently lowered by addition of an acid or buffer. A suitable carbohydrate is then dissolved in the solution and the solution is lyophilized to dryness to form a lyophilized powder or cake.

Tigecycline may be blended with a suitable carbohydrate and dissolved in water. After the pH of the solution is adjusted so that it is acidic, the solution may then be lyophilized to dryness to form a lyophilized powder or cake.

Lyophilization of solutions of the invention may be accomplished by any pharmaceutically acceptable means. Once lyophilized, compositions of the invention may be stored under an inert gas, such as nitrogen, to further slow the degradation process, but, unlike the current tigecycline composition, such low oxygen environments are not necessary for the invention.

When tigecycline is combined with a suitable carbohydrate, any solid-state form of tigecycline that is sufficiently soluble in water may be used. Such solid-state forms include crystalline tigecycline polymorphs, amorphous forms, and salts.

Additionally, when preparing tigecycline solutions of the invention for lyophilization, one adds sufficient acid or buffer to the aqueous solution containing tigecycline to obtain a pH from about 3.0 and about 7.0 including from about 4.0 to about 5.0 and from about 4.2 to about 4.8.

The compositions of the invention may be prepared for single-dosage use. In this embodiment, the solutions of the invention are lyophilized in individual vials, such as 20 ml vials. Upon lyophilization, the vials are stoppered with any pharmaceutically acceptable stopper. The stoppered vials are then shipped for use.

When needed, the vials can be reconstituted by adding sufficient diluent to achieve the desired concentration of tigecycline. The concentration of reconstituted solutions may be easily determined by those of ordinary skilled in the art. Any pharmaceutically acceptable diluent may be used. Examples of such diluents include water, saline, such as 0.9% saline, Lactated Ringer's Injection solution and dextrose solutions including 5% dextrose (D5W).

Reconstituted solutions of the invention may then be stored in a reconstituted state, unlike current compositions, prior to admixture. Admixture can occur, for example, in an intravenous bag. To prepare an admixture, sufficient reconstituted solution is mixed in an intravenous bag containing a pharmaceutically acceptable diluent such as saline solution or dextrose solution such as D5W. The concentration of admixtures may be easily determined by those of ordinary skill in the art. Admixture times for compositions of the invention can be much longer than those of the existing composition. Once admixed, the tigecycline solution is ready for patient administration. The admixture may be administered alone or together with another pharmaceutical agent or composition.

The following six examples illustrate various embodiments of the invention and are not intended to limit the invention in any way. Each example details several experiments where tigecycline was dissolved with a carbohydrate in aqueous acidic solution, lyophilized, and analyzed for degradation

products by HPLC. The HPLC conditions for each example were essentially the same. The tables accompanying the examples reflect the results of the HPLC data which show the oxidative degradation products identified in the tables as relative retention times (RRT) 0.50/MW 601 and RRT 0.55/MW 583, the epimer (RRT 0.74/MW 585), and the total amount of tigecycline present under a variety of conditions (identified as "Tigecycline" in the tables"). In many instances, after the solutions were lyophilized, they were placed under accelerated stability conditions of 40° C. and 75% relative humidity. These conditions are industry standards used for simulating the effect of long-term storage under normal shelf conditions.

In example 1, solutions of tigecycline, lactose, and 1.0 N HCl were lyophilized and the resulting cakes were placed in stability chambers at 40° C. and 75% relative humidity for 25 days. At the end of the 25 days, the cakes were analyzed by HPLC to identify degradation products.

A similar experiment is detailed in Example 2a. There, the lyophilized cakes were analyzed by HPLC after being stored for 39 days at 40° C. and 75% relative humidity. Sample cakes from two of the experiments were reconstituted in D5W (5% dextrose) and samples from the remaining cakes were reconstituted in saline immediately prior to HPLC analysis.

In experiment 2b, after the lyophilized cakes were stressed as per the conditions in example 2a, several of the cakes were reconstituted in 0.9% saline and kept in solution for 6 hours. Others were reconstituted in dextrose. At the end of the 6 hour period, some of these solution samples, as identified in table 2b, were tested by HPLC.

Example 2c illustrates a stability test on admixed solutions. In these solutions, the reconstituted solutions of example 2b were held for 6 hours at about 10 mg/mL and then diluted to about 1 mg/mL, the typical intravenous concentration for tigecycline, and held for 18 hours prior to analysis by HPLC (table 2c).

In example 3, gentisic acid, rather than hydrochloric acid, was used to reduce the pH of the pre-lyophilized solutions of tigecycline. Once lyophilized, the cakes were stressed at 45° C. and 75% relative humidity for 48 days and then analyzed by HPLC.

The samples of example 4 show the effects of changing from lactose to other carbohydrates on epimer formation and tigecycline recovery when making the pre-lyophilized tigecycline solutions. In each of examples 4a, 4b, and 4c, the indicated solutions were prepared and lyophilized. Each cake was stressed according to the parameters provided in examples 4a-4c, taken into solution, and analyzed by HPLC.

Hold time, the time in between compounding and lyophilization, and order of tigecycline and lactose addition were studied as factors in epimer formation and tigecycline recovery in example 5. Once the cakes were lyophilized, they were stressed at 40° C. and 75% relative humidity for 48 days prior to HPLC analysis. Summaries of the HPLC data appear in table 5.

The ratio of lactose to tigecycline was varied in the experiments in example 6. When preparing the solutions to be lyophilized, varying ratios of lactose to tigecycline were employed. The mass ratios are reported in the first column of table 6. The solutions, which each had a pH of about 5.0, were subsequently lyophilized to dryness and the resulting cakes were stressed at 40° C. and 75% relative humidity for 20 days and analyzed by HPLC.

EXAMPLE 1

Tigecycline (1880 mg) was dissolved in 75 ml of Milli-Q water to form a bulk solution. An aliquot from this bulk solution containing approximately 100 mg of tigecycline was dissolved into a 20 ml vial containing 200 mg of lactose monohydrate. Another aliquot of the bulk solution containing approximately 100 mg of tigecycline was placed into an empty 20 ml sample vial. No pH adjustment was made to either of these two solutions. The solutions were subsequently lyophilized to dryness.

The pH of the remaining bulk solution was lowered to about 6.0 with the addition of 1.0N HCl. Once a pH of about 6.0 was obtained, an aliquot from the bulk solution containing about 100 mg of tigecycline was dissolved into a 20 ml sample vial containing about 200 mg of lactose monohydrate and the resulting solution was lyophilized to dryness. The remaining bulk solution was treated with 1.0N HCl until a pH of about 5.5 was obtained at which point 100 mg of tigecycline from the bulk solution was transferred into a 20 ml vial containing 200 mg of lactose monohydrate. After dissolution, the solution was lyophilized to dryness. Similarly, 20 ml sample vials containing solutions of about 100 mg of tigecycline and about 200 mg of lactose were prepared at pHs of about 5.0 and about 4.5. Another solution sample was prepared at about pH 4.5 without any lactose. In each case, the solutions were subsequently lyophilized to dryness. All lyophilizations were done on solutions frozen at −70° C. by dry ice with acetone.

The lyophilized samples were placed in a 40° C. /75% RH chamber for 25 days. Afterwards, the samples were analyzed by HPLC and a summary of the results appears below in table 1, which reflects the major degradation products for each cake that was tested. The sum total of the 6 major degradation products listed in the tables does not equal 100% because not all degradation products are listed in the table. Of the 7 cakes tested in example 1, 5 were compositions of the invention and the first two (tigecycline alone without pH adjustment and tigecycline plus lactose without pH adjustment) were controls.

The advantages of the compositions of the invention are apparent from this example. For instance, in the composition prepared without lactose at a pH of about 4.5, only 74.10% tigecycline was detected whereas the epimer was present in an amount of 23.51%. By comparison, the pH 4.5 sample with lactose contained only 2.53% epimer and had a tigecycline content of 97.17%.

TABLE 1

	RRT					
	0.5	0.55	Epimer 0.74	1.25	1.67	Tigecycline
			MW			
Sample ID	601	583	585	528	556	585
Tigecycline only (no pH adjustment)	0.57	2.15	6.50	2.50	1.72	80.59
Tigecycline + lactose (no pH adjustment)	0.61	0.48	1.05	0.71	1.05	91.95
pH6.0 + lactose	0.04	0.15	2.56	0.04	0.12	96.83
pH5.5 + lactose	0.01	0.11	2.54	0.01	0.04	97.07
pH5.0 + lactose	0.01	0.04	2.43	ND	0.02	97.27
pH 4.5 (no lactose)	0.11	0.21	23.51	0.14	0.16	74.10
pH 4.5 + lactose	0.01	0.05	2.53	ND	0.01	97.17

ND = Not detected;
MW is molecular weight;
RRT means relative retention time to tigecycline peak.

EXAMPLE 2

2a. Tigecycline (1700 mg) was dissolved in 85 ml of Milli-Q water to form a bulk solution. Solutions containing about 100 mg of tigecycline and about 200 mg of lactose monohydrate were prepared at pHs of about 5.2, 5.0, 4.8, and 3.0 in the same manner that tigecycline/lactose/HCl solutions were prepared in example 1. A solution of tigecycline and lactose at pH of about 4.5 was prepared by adding 1.0 N NaOH to the bulk solution at pH 3.0 followed by dissolving an aliquot of bulk solution containing about 100 mg of tigecycline into a 20 ml vial containing about 200 mg of lactose monohydrate. All samples were lyophilized (frozen at −50° C. by freeze dryers from AdVantageNirtis) to dryness. The lyophilized samples were placed in a 40° C./75% RH chamber for 39 days and sub-sampled and analyzed by HPLC. The data are shown in table 2a.

2b. At the end of 39 days, the lyophilized cakes of Example 2a were reconstituted with 0.9% NaCl to a concentration of 10 mg/ml of tigecycline and kept at room temperature for 6 hours. Separate aliquots of the solutions at pH of about 5.0 and about 4.5 were reconstituted with 5% Dextrose, instead of saline, to a concentration of about 10 mg/ml and kept at room temperature for 6 hours. Each of the solutions was then analyzed by HPLC, and the results are shown in Table 2b.

The data show that the compositions of the invention protect against epimer formation in reconstituted solutions for 6 hours. Indeed, the maximum epimer content of any one of these examples was only 2.45%, whereas the minimum tigecycline content was 97.1%. In one embodiment, where the pH was about 4.5 and the diluent was saline, at the end of the 6 hour reconstitution period, only 1.60% of epimer was present. In that embodiment, the amount of tigecycline was measured to be 98.15%, which, in some applications, may be of sufficient purity for hospital use.

2c. Admixture solutions of tigecycline (at 1 mg/ml) were made by diluting the reconstituted solution (from example 2b) with 0.9% NaCl or 5% Dextrose depending upon which diluent was used for reconstitution. The solutions were then kept at room temperature for 18 hours and analyzed by HPLC. The results are summarized in Table 2c.

The sample at about pH 4.5 with lactose and without dextrose had its epimer concentration increase from 1.60% to only 1.80% on going from reconstitution to admixture whereas the overall tigecycline content decreased only slightly for that sample from 98.15% to 97.97%. These results on the about pH 4.5 sample illustrate that that sample is sufficiently stable after the lyophilized cake is stored under accelerated stability conditions for 39 days followed by 6 hours of reconstitution and 18 hours of admixture.

TABLE 2a

	RRT					
	Epimer					
	0.5	0.55	0.74	1.25	1.67	Tigecycline
	MW					
Sample ID	601	583	585	528	556	585
pH 5.2 + lactose	0.01	0.08	2.21	ND	ND	97.58
pH 5.0 + lactose	0.01	0.07	2.20	ND	0.01	97.57
pH 5.0 + lactose in 5% dextrose	0.01	0.08	2.21	ND	0.01	97.38
pH 4.8 + lactose	0.01	0.02	2.15	ND	ND	97.63
pH 4.5 + lactose	0.01	0.03	1.37	ND	0.01	98.42
pH 4.5 + lactose in 5% dextrose	0.01	0.02	1.35	ND	ND	98.23
pH 3.0 + lactose	0.01	0.02	1.34	ND	ND	98.49

TABLE 2b

	RRT					
	Epimer					
	0.5	0.55	0.74	1.25	1.67	Tigecycline
	MW					
Sample ID	601	583	585	528	556	585
pH 5.2 + lactose	0.01	0.12	2.31	0.01	0.04	97.37
pH 5.0 + lactose	0.01	0.10	2.37	ND	0.03	97.33
pH 5.0 + lactose in 5% dextrose	0.01	0.10	2.45	0.01	0.03	97.10
pH 4.8 + lactose	0.01	0.09	2.32	ND	0.02	97.41
pH 4.5 + lactose	0.01	0.09	1.60	0.01	0.02	98.15
pH 4.5 + lactose in 5% dextrose	0.01	0.08	1.65	ND	0.01	97.96
pH 3.0 + lactose	0.01	0.06	2.10	ND	ND	97.70

TABLE 2c

	RRT					
	Epimer					
	0.5	0.55	0.74	1.25	1.67	Tigecycline
	MW					
Sample ID	601	583	585	528	556	585
pH 5.2 + lactose	0.01	0.05	2.49	0.01	0.09	97.11
pH 5.0 + lactose	0.01	0.06	2.57	0.01	0.06	97.09
pH 5.0 + lactose in 5% dextrose	0.02	0.05	2.80	0.01	0.06	96.66
pH 4.8 + lactose	0.02	0.04	2.52	0.01	0.04	97.19
pH 4.5 + lactose	0.01	0.03	1.80	ND	0.03	97.97
pH 4.5 + lactose in 5% dextrose	0.02	0.02	2.02	ND	0.02	97.56
pH 3.0 + lactose	0.01	0.04	2.72	ND	ND	97.13

EXAMPLE 3

Tigecycline (700 mg) was dissolved in 28 ml of Milli-Q water to form a bulk solution. An aliquot of the bulk solution containing about 100 mg of tigecycline was loaded into a 20 ml vial as control sample. Solution samples of tigecycline, lactose, and an acid were prepared at pHs of about 5.8, 5.1, and 4.5 according to the methods of example 1 except that gentisic acid was used to lower the pH of the bulk solution rather than 1.0 N HCl. An additional two samples of tigecycline solutions without lactose were prepared, one at a pH of about 5.1 and another at a pH of about 4.5. All of the solutions were frozen at −70° C. (by dry ice with acetone) and lyophilized to dryness. The lyophilized samples were placed in a 40° C./75% RH chamber for 48 days and analyzed by HPLC. The data are summarized in Table 3 and show that this composition works according to the invention to reduce degradation.

TABLE 3

	RRT					
	Epimer					
	0.5	0.55	0.74	1.25	1.67	Tigecycline
	MW					
Sample ID	601	583	585	528	556	585
Control	0.37	2.17	7.37	1.50	1.47	81.13
pH 4.5 no lactose	0.02	0.05	28.11	0.04	0.02	71.37

TABLE 3-continued

	RRT					
	0.5	0.55	Epimer 0.74	1.25	1.67	Tigecycline
			MW			
Sample ID	601	583	585	528	556	585
pH 4.5 + lactose	0.01	0.02	6.32	ND	ND	93.42
pH 5.1 no lactose	0.05	0.10	20.90	0.10	0.08	77.87
pH 5.1 + lactose	0.01	0.02	3.94	ND	0.02	95.82
pH 5.8 no lactose	0.04	0.13	17.38	0.21	0.21	81.31

EXAMPLE 4

4a. Tigecycline (1600 mg) was dissolved in 64 ml of Milli-Q water to form a bulk solution and two samples from the solution, each containing about 100 mg of tigecycline, were loaded into two separate sample 20 ml sample vials containing 160 mg of lactose monohydrate and 160 mg mannitol respectively. A third sample containing about 100 mg of tigecycline from the bulk solution was loaded into a blank 20 ml vial. The pH of the remainder of the bulk solution was sequentially adjusted with 1.0N HCl to about 7.0, 6.5, and 6.0 as per the procedure outlined in example 1. Sample solutions each containing about 100 mg tigecycline were loaded into 20 ml vials containing 160 mg of lactose monohydrate, 160 mg of mannitol, or neither at each pH value. The resulting solutions were lyophilized (frozen at −70° C. by dry ice with acetone) to dryness. The lyophilized samples were placed in a 40° C. oven for 70 hours and then analyzed by HPLC. The data are summarized in table 4a.

4b. Tigecycline (1800 mg) was dissolved in 72 ml of Milli-Q water to form a bulk solution. Aliquots from the bulk solution containing about 100 mg of tigecycline were loaded into three separate 20 ml vials containing about 200 mg of lactose monohydrate, fructose, and sucrose respectively. The pH of the bulk solution was sequentially adjusted with 1.0N HCl to about 6.0 and 5.4 according to the procedure outlined in example 1. At each pH value, aliquots of solution containing about 100 mg of tigecycline were taken into 20 ml vials containing 200 mg of one of the following carbohydrates:

lactose monohydrate, fructose, or sucrose and dissolved. Solutions without carbohydrates were also prepared at each pH value. The solutions were lyophilized (frozen at −70° C. by dry ice with acetone) to dryness. The lyophilized samples were placed in a 40° C. oven for 89 hours and analyzed by HPLC. The results are summarized in Table 4b.

4c. Tigecycline (1000 mg) was dissolved in 50 ml of Milli-Q water to form a bulk solution. The pH of the bulk solution was adjusted with 1.0N HCl to about 5.0. Four aliquots of bulk solution, each containing about 100 mg of tigecycline, were loaded into 20 ml vials containing about 200 mg of glucose, mannose, ribose, and xylose respectively and dissolved. A fifth aliquot of bulk solution containing about 100 mg of tigecycline was loaded into a 20 ml vial containing about 125 mg of threose and dissolved. All five solutions were lyophilized (frozen at −50° C. by freeze dryers from AdVantageNirtis) to dryness. The lyophilized samples were placed in a 25° C./60% RH chamber for 42 days and analyzed by HPLC. The results are summarized in table 4c. Data in tables 4a-4c are meant to illustrate the effect of suitable carbohydrates such as lactose on the invention.

TABLE 4a

	RRT					
	0.5	0.55	Epimer 0.74	1.25	1.67	Tigecycline
			MW			
Sample ID	601	583	585	528	556	585
Tigecycline only	0.03	0.07	1.08	ND	0.07	98.51
pH 7.0	0.03	0.06	1.15	0.02	0.09	98.35
pH 6.5	0.03	0.06	1.73	0.02	0.09	97.78
pH 6.0	0.02	0.06	2.69	0.02	0.08	96.82
Tigecycline + lactose	0.03	0.10	0.89	ND	0.07	98.33
pH 7.0 + lactose	0.03	0.08	0.94	ND	0.06	98.45
pH 6.5 + lactose	0.02	0.05	0.91	ND	NA	98.50
pH 6.0 + lactose	ND	0.04	0.90	ND	NA	98.54
Tigecycline + mannitol	0.05	0.13	1.40	ND	0.14	97.69
pH 7.0 + mannitol	0.05	0.11	1.80	ND	0.12	97.45
pH 6.5 + mannitol	0.03	0.08	2.28	ND	0.08	96.98
pH 6.0 + mannitol	0.02	0.06	2.56	ND	0.07	96.82

TABLE 4b

	RRT					
	0.5	0.55	Epimer 0.74	1.25	1.67	Tigecycline
			MW			
Sample ID	601	583	585	528	556	585
Tigecycline only	0.04	0.12	1.06	0.04	0.12	98.39
pH 6.0	0.03	0.09	2.72	0.03	0.08	96.90
pH 6.0 + lactose	0.01	0.04	0.97	ND	0.03	98.76
pH 5.4 + lactose	0.01	0.06	1.01	0.01	0.03	98.71
pH 6.0 + fructose	0.04	0.09	17.70	0.02	0.02	81.92
pH 6.0 + sucrose	0.01	0.08	1.38	0.02	0.03	98.32

TABLE 4c

	RRT					
	0.5	0.55	Epimer 0.74	1.25	1.67	Tigecycline
			MW			
Sample ID	601	583	585	528	556	585
pH 5.0 + glucose	0.01	0.06	1.02	ND	0.01	98.81
pH 5.0 + mannose	0.01	0.06	1.23	ND	ND	98.60
pH 5.0 + ribose	0.44	0.02	33.30	ND	0.01	65.94
pH 5.0 + xylose	0.02	0.09	18.05	ND	ND	81.68
pH 5.0 + threose	0.91	3.41	7.00	0.07	0.79	22.85

EXAMPLE 5

5a. Tigecycline (1000 mg) was dissolved in 40 ml of Milli-Q water to form a bulk solution. The pH of the bulk solution was adjusted with 1.0N HCl to about 5.0. At that pH, two aliquots of the bulk solution, each containing about 100 mg tigecycline, were loaded separately into two 20 ml vials each containing about 200 mg lactose monohydrate. One sample was frozen immediately at −70° C. (by dry ice with acetone), and the other sample was kept at room temperature for 5 hours before freezing. Frozen samples were subsequently lyophilized to dryness. The lyophilized samples were

placed in a 40° C./75% RH chamber for 48 days and analyzed by HPLC. The results are summarized in Table 5 as the "A" samples.

5b. Lactose monohydrate (750 mg) was dissolved in 15ml of Milli-Q water. Tigecycline (375mg) was added to this solution and the pH was adjusted to about 5.0 with 1.0N HCl. At this pH, two aliquots from the solution, each containing about 100 mg of tigecycline and about 200 mg of lactose monohydrate, were loaded into two 20 ml vials respectively. The solution in one sample vial was frozen immediately at −70° C. (by dry ice with acetone). The solution in the other sample was kept at room temperature for 5 hours before freezing. Frozen samples were lyophilized to dryness. The lyophilized samples were placed in a 40° C./75% RH chamber for 48 days and analyzed by HPLC. The results are summarized in Table 5 as the "B" samples. The "A" and "B" data illustrate compositions of the invention reducing degradation products.

TABLE 5

	RRT					
	Epimer					
	0.5	0.55	0.74	1.25	1.67	Tigecycline
	MW					
Sample ID	601	583	585	528	556	585
A (lactose dissolved in tigecycline)	0.01	0.02	3.18	0.01	0.02	96.57
B (tigecycline dissolved in lactose)	0.00	0.02	3.32	ND	0.01	96.43
A left in RT for 5 hrs before freeze	0.01	0.03	5.67	0.02	0.02	94.03
B left in RT for 5 hrs before freeze	0.01	0.02	3.82	ND	0.02	95.86

EXAMPLE 6

6a. Tigecycline (1700 mg) was dissolved in 85 ml of Milli-Q water to form a bulk solution. The pH of the bulk solution was adjusted to about 5.0 with 1.0N HCl. Four aliquots of the bulk solution, each containing about 100 mg tigecycline, were loaded separately into four 20 ml vials containing about 50, 100, 200, and 300 mg of lactose monohydrate respectively. Once the lactose completely dissolved, the samples were lyophilized (frozen at −50° C. by freeze dryers from AdVantageNirtis) to dryness. The lyophilized samples were placed in a 40° C. 75% RH chamber for 4 days and analyzed by HPLC. The results are summarized in Table 6a and give examples of compositions of the invention.

6b. Tigecycline (400 mg) was dissolved in 20 ml of Milli-Q water to form a bulk solution. The pH of the bulk solution was adjusted to about 5.0 with 1.0N HCl. Three aliquots of the bulk solution, each containing about 100 mg tigecycline, were loaded separately into three 20 ml vials containing 15, 31, and 62 mg lactose monohydrate respectively. Upon dissolution, the samples were lyophilized (frozen at −50° C. by freeze dryers from AdVantage/Virtis) to dryness. The lyophilized samples were placed in a 40° C./75% RH chamber for 20 days and analyzed by HPLC. The results are summarized in Table 6b and show compositions of the invention.

TABLE 6a

	RRT					
	Epimer					
	0.5	0.55	0.74	1.25	1.67	Tigecycline
	MW					
Sample ID	601	583	585	528	556	585
(molar ratio)						
pH 5.0 + lactose 50 mg (1:0.81)	ND	0.04	1.01	ND	ND	98.53
pH 5.0 + lactose 100 mg (1:1.62)	ND	0.04	0.82	ND	ND	98.73
pH 5.0 + lactose 200 mg (1:3.25)	ND	0.04	0.82	ND	ND	98.69
pH 5.0 + lactose 300 mg (1:4.87)	ND	0.04	0.87	ND	ND	98.64

TABLE 6b

	RRT					
	Epimer					
	0.5	0.55	0.74	1.25	1.67	Tigecycline
	MW					
Sample ID	601	583	585	528	556	585
(molar ratio)						
pH 5.0 no lactose	0.03	0.07	5.40	0.02	0.07	94.19
pH 5.0 + lactose 15 mg(1:0.24)	0.02	0.04	3.83	0.01	0.05	95.87
pH 5.0 + lactose 31 mg(1:0.50)	0.01	0.03	3.02	ND	0.03	96.72
pH 5.0 + lactose 62 mg (1:1.00)	0.01	0.03	2.18	ND	0.02	97.61

What is claimed is:

1. A composition comprising tigecycline, lactose, and an acid selected from hydrochloric acid and gentisic acid, wherein the molar ratio of tigecycline to lactose is between about 1:0.2 and about 1:5 and the pH of the composition in a solution is between about 3.0 and about 7.0.

2. The composition of claim **1** wherein the composition is lyophilized.

3. The composition of claim **1** wherein the composition is in solid form.

4. The composition of claim **1** wherein the pH of the composition in a solution is between about 4.0 and about 5.0.

5. The composition of claim **4** wherein the pH of the composition in a solution is between about 4.2 and about 4.8.

6. The composition of claim **1** wherein the acid is hydrochloric acid.

7. The composition of claim **2** wherein the acid is hydrochloric acid.

8. The composition of claim **3** wherein the acid is hydrochloric acid.

9. The composition of claim **1** wherein the molar ratio of tigecycline to lactose is between about 1:1.6 and about 1:3.3.

10. The composition of claim **1** wherein the pH of the composition in a solution is between about 4.5 and about 6.0.

11. The composition of claim **1** wherein the pH of the composition in a solution is between about 4.5 and about 5.5.

12. A composition comprising tigecycline, lactose, and hydrochloric acid, wherein the molar ratio of tigecycline to lactose is between about 1:0.2 and about 1:5 and the pH of the composition in a solution is between about 3.0 and about 7.0.

13. The composition of claim **12** wherein the molar ratio of tigecycline to lactose is between about 1:1.6 and about 1:3.3.

14. The composition of claim **12** wherein the pH of the composition in a solution is between about 4.0 and about 5.0.

15. The composition of claim **14** wherein the pH of the composition in a solution is between about 4.2 and about 4.8.

16. The composition of claim **12** wherein the pH of the composition in a solution is between about 4.5 and about 6.0.

17. The composition of claim **16** wherein the pH of the composition in a solution is between about 4.5 and about 5.5.

18. The composition of claim **12** wherein the composition is in solid form.

19. The composition of claim **13** wherein the composition is in solid form.

20. The composition of claim **14** wherein the composition is in solid form.

21. The composition of claim **15** wherein the composition is in solid form.

22. The composition of claim **16** wherein the composition is in solid form.

23. The composition of claim **17** wherein the composition is in solid form.

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CERTIFICATE OF SERVICE

I certify that, on October 29, 2015, this Corrected Opening Brief for Appellant was filed electronically using the CM/ECF system, which will serve the brief on all counsel of record.

/s/ Robert Greenfeld

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CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of Fed. R. App. P. 28.1(e)(2)(B) because this brief contains 6,263 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii) and Fed. Cir. R. 32(b), as counted by Microsoft® Word 2010, the word processing software used to prepare this brief.

This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) or Fed. R. App. P. 28.1(e) and the type style requirements of Fed. R. App. P. 32(a)(6) because this brief has been prepared in a proportionally spaced typeface using Microsoft® Word 2010, Times New Roman, 14 point.

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